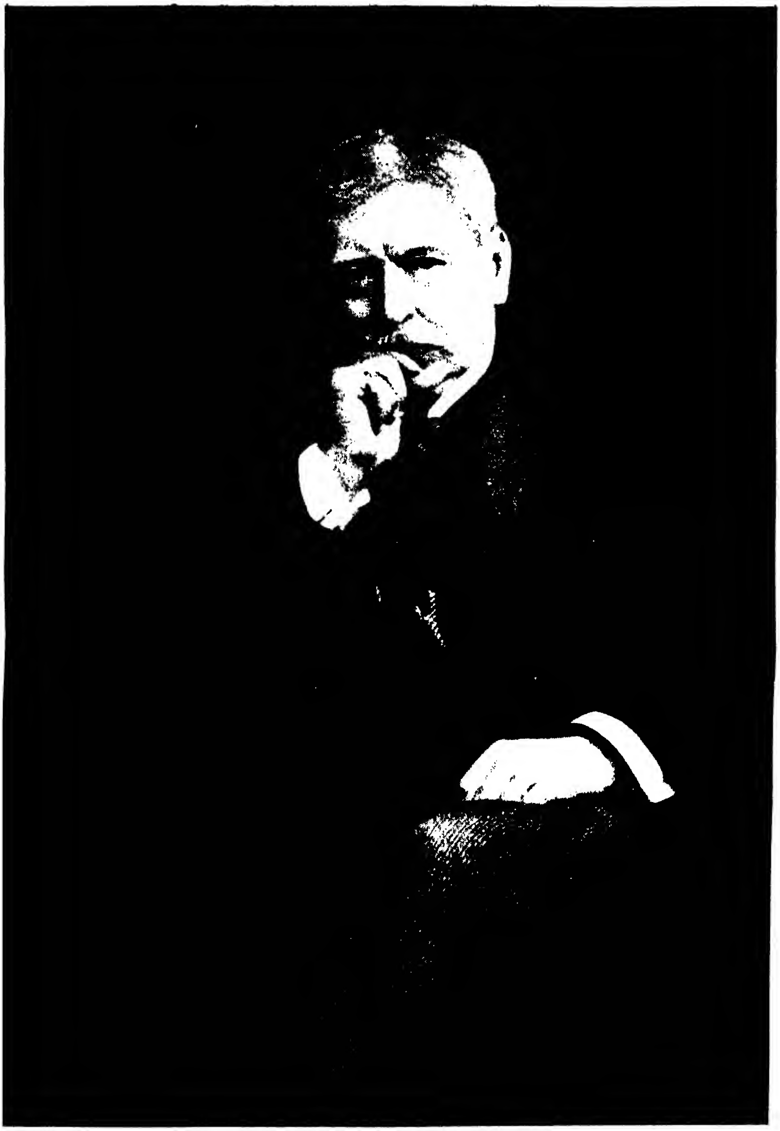
MANSON'S
TROPICAL DISEASES



SIR PATRICK MANSON, G.C.M.G., F.R.S.

PLATE I

MANSON'S TROPICAL DISEASES

A MANUAL OF THE DISEASES OF WARM CLIMATES

EDITED BY

PHILIP H. MANSON-BAHR

C.M.G., D.S.O., M.A., M.D., D.T.M. AND H. CANTAB., F.R.C.P. LOND.

Senior Physician to the Hospital for Tropical Diseases, London, the Albert Dock Hospital and the Tilbury Hospital; Consulting Physician to the Colonial Office and Crown Agents for the Colonies; Consultant in Tropical Diseases to the Royal Air Force; Director, Division of Clinical Medicine, London School of Hygiene and Tropical Medicine; Lecturer on Tropical Medicine to the London Hospital, the West London Post-Graduate College, and the North-Eastern Post-Graduate College; Corresponding Member of the Société de Pathologie Exotique; Member of the Washington Academy of Medicine; late Examiner in Tropical Medicine to the Conjoint Board of the Royal College of Physicians and Royal College of Surgeons, England, and to Cambridge and Hongkong Universities. Author (with A. Alcock) of "The Life and Work of Sir Patrick Manson," 1927; and "The Dysenteric Disorders," 1939.

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PREFACE TO THE ELEVENTH EDITION

To preserve Manson's Tropical Diseases as a serviceable manual for the practitioner in the tropics, fulfilling at the same time the purpose of a résumé of scientific progress in an ever-widening sphere of activity, is admittedly no easy matter.

Progress, so rapid and on such an increasing scale, necessitates complete revision of this book every three or four years. The Editor, though conscious of his limitations, has endeavoured once again to the best of his ability, to carry out his original aim in this the fifth of the series to which he has set his hand since he assumed the responsibility of Editorship, after the death of Sir Patrick Manson.

On this occasion, he has taken the opportunity of deleting much ancient history in the text and including, in its place, chapters on the preparation for life in the tropics. In addition, he has attempted to summarize in a concise form the influence of a tropical environment in altering or moulding the facies of common diseases encountered in ordinary practice. In this connection he would stress the fact, often not as much appreciated as it should be, that, in dealing with the disease in the tropics the practitioner is often faced with a composite problem, due to the existence of multiple and diverse parasitic infections in the same patient, and the fact that the symptomatology of some of the commoner systemic diseases may become masked or disguised by some superadded protozoal or helminthic infection. For these reasons the diagnosis, and consequently the treatment, of diseases in the tropics may become much more complicated and involved than would be the case in non-tropical countries.

The greater attention that is being given to nutrition, which

it is now realized lies at the root of many human ills, has necessitated the inclusion of the elements of this subject in a general survey of life in the torrid zone. It is felt that this new departure will be welcomed by many.

Several sections, notably those of yellow fever and typhus, have undergone very considerable revision, whilst other chapters, such as those on technique, have been omitted in order to make room for new matter. The malaria chapter has been drastically pruned of non-essential elements, and the zoological aspects of the causative parasites relegated to the Appendix, where they properly belong.

The Editor is conscious of the debt he owes to correspondents in every part of the world for many helpful suggestions and improvements, to all of which he has paid the attention they deserve. Though he has made himself responsible for the whole of this revision, he would take this opportunity of thanking Dr. G. W. Marshall Findlay, C.M.G., once more for his valued help in connection with the virus diseases, and also Dr. Russell Amies, who has given similar assistance with the smallpox group.

He would also acknowledge the continued loyal co-operation of Mr. W. J. Muggleton, M.S.M., with whom he has been associated for so many years.

Finally, he is deeply appreciative of the reception which has been given to Manson's Tropical Diseases throughout its long career.

PHILIP MANSON-BAHR.

149, *Harley Street, W.*1.
January, 1940.

NOTE.

In scientific textbooks and in those devoted to materia medica, the term " millitre," or " mil " is being employed instead of the " c.c." The " mil " is now adopted as the official standard in England, but it has not been used in this book as the term is not yet recognized internationally, nor do the " mil " and the " c.c." represent identical amounts.

Throughout this book, whenever possible, the equivalents are given in the apothecaries' and metric systems.

PREFACE TO THE FIRST EDITION

A MANUAL on the diseases of warm climates, of handy size, and yet giving adequate information, has long been a want; for the exigencies of travel and of tropical life are, as a rule, incompatible with big volumes and large libraries. This is the reason for the present work.

While it is hoped that the book may prove of practical service, it makes no pretension to being anything more than an introduction to the important department of medicine of which it treats; in no sense is it put forward as a complete treatise, or as being in this respect comparable to the more elaborate works by Davidson, Scheube, Rho, Laveran, Corre, Roux, and other systematic writers in the same field.

The author avails himself of this opportunity to acknowledge the valuable assistance he has received, in revising the text, from Dr. L. Westenra Sambon and Mr. David Rees, M.R.C.S., L.R.C.P., Superintendent, London School of Tropical Medicine. He would also acknowledge his great obligation to Mr. Richard Muir, Pathological Laboratory, Edinburgh University, for his care and skill in preparing the illustrations.

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CHAPTER I

LIFE IN THE TROPICS

GENERAL OBSERVATIONS

It is difficult to define in exact terms what is meant by "a complete method of assessment of fitness for life in the tropics." There should be an attempt to sum up the individual in all his aspects, not only as regards fitness of the body and internal organs to withstand the strain of tropical conditions, but taking into account also his nervous system and ability to remain stable and serene in the face of privations and petty provocations. This may seem a counsel of perfection, yet it is unquestionably true that in this, as in other circumstances, character and temperament are all-important, the correct estimation of which is a matter of judgment, and of judgment alone, since we do not possess a single reliable test to indicate the reactions of the individual to such changed environment. Experience therefore is the only guide, and the question is one which agitates the minds of those who sit on Selection Boards and of other bodies charged with this responsibility.

It is by no means always true that the obviously athletic, physically-developed individual stands up to the isolation and totally changed environment, in which he necessarily finds himself, as well as another who may be more mediocre, both in physique and upbringing. On the whole, it may be said that the attainment of a certain degree of toughness, with a capacity for roughing it, together with that innate instinct of fending for oneself, which is so often exhibited in the hardy northern races, is a much more suitable preparation than the sheltered life enjoyed by many of the educated young people of the present day. The main requirement is *adaptability*, and this almost undefinable quality is met with mainly in those whose path through life has not been rendered too smooth. This applies mainly to men, but is true in a lesser degree in the case of women.

The best kind of mind for tropical life is one of an enquiring nature: one which takes an interest in the people and things around; in fact the type of person best fitted for this kind of existence is one who has

a passion for hobbies of all sorts, and if a particular hobby should be his life's work, he is all the more fortunate. Such a one is not unduly sensitive to the "slings and arrows of outrageous fortune." A good mixer and socially inclined towards his own race, he nevertheless shows a sympathetic and understanding attitude to his native associates.

In this assessment of mental suitability, it is important that the antecedents of the applicant should be scanned in all their bearings. Thus it is essential to enquire into family, upbringing, school, University career, etc., the idea being to discover, not so much the scholarly and athletic prowess of the candidate, as his general bearing towards his fellows, and to reveal the existence of complexes and fads which would militate against his success abroad. The tropics is no place for the highly-strung, or persons of a neurotic tendency. In the case of young men it is inevitable that the question of alcohol consumption, excessive smoking and other deleterious habits should be raised. This, naturally, is often a delicate matter, but it is so vitally important that even if there is a suspicion of excess, the candidate is thereby unfitted for tropical service, in that what might constitute a minor evil in civil life in temperate zones may constitute a vice under the more exacting conditions of the tropics. It must be understood that no implication is intended that the strict teetotaller is any more fitted than the one oppositely inclined. The emphasis is on moderation and self-control. The standard of fitness should be estimated individually: no hard-and-fast rules can be laid down.

The *age* of the candidate is obviously an important consideration, and in this connection there is some general agreement. He or she should have attained to maximum development before going out. Those under twenty-one—and this is true especially of women—withstand extreme heat and humidity badly, and appear, moreover, to be more susceptible to tropical diseases. Women should be fully matured in mind as well as in body and, as a rule, their age should be somewhat higher than for men, viz. from twenty-three to twenty-five. It is a matter of observation that men over forty find it very difficult to accustom themselves to intense heat, though exceptions will readily occur to the mind such as Robert Koch, a pioneer in medical science, and Abel Chapman in zoology. Both had already passed the limit stated ere they set foot in Central Africa, and found themselves equal to its exacting demands.

While, as to *height and weight* there can be no absolute standard, the amount of deviation from the generally accepted averages should not be great. As a rule, spareness is more desirable than plumpness. Certainly the tropics is no place for the positively fat man. The "lanky," spare type is best suited to tropical conditions, and the dark-haired, brown-eyed and dark-complexioned is generally considered more fitted than the blue-eyed, fair-haired, tender-skinned "Norse" or "Aryan" type. It is generally assumed that the brunette southern type with increased pigmentation of the skin is thus endowed as a

protection against heat, but here again, it must not be thought that there are not exceptions to this rule.

PASSING CANDIDATES FOR THE TROPICS

The standard adopted for passing candidates for life in the tropics need not necessarily be as high as that required for military purposes or for the Royal Air Force. Nevertheless, a certain degree of fitness should be aimed at. The candidate must therefore be examined from head to foot.

Teeth.—As the food in the tropics is neither so palatable nor so easily masticated as in the comparatively luxurious conditions at home, special attention must be paid to the masticatory apparatus. Teeth must reach a high standard, and candidates with universally carious teeth or incomplete dentine should be eliminated. Everyone who proposes to go to the tropics should have his mouth put in order, because dental decay takes place in intense heat more rapidly than elsewhere, and it is quite unfair to blame regular quinine prophylaxis for any share in this process. There cannot be any objection to dentures, provided that the owner possesses a spare set, and that they are adequate and comfortable.

Nose and throat.—Special care should be directed to the tonsils. If they are enlarged and septic they must be enucleated prior to tropical service. Subjects of post-nasal catarrh and chronic granular pharyngitis do not do well. Sinus trouble does not improve in the tropics and, as regards North and West Africa, where sandstorms are commonly encountered, persons suffering from chronic antral disease should be discarded.

Eyes and ears.—A reasonable degree of visual acuity is essential. Opinions differ considerably regarding the extent of visual deficiency which may be passed over. The Editor is of the opinion that grave refractive errors are deleterious, and under certain circumstances, candidates with a degree of myopia about — 6D should be rejected. No candidate having high myopia is suited for a bush, or isolated station. If glasses must be worn, then the wearer must provide himself with spare sets. Crookes's lemon-tinted lenses are of value in diminishing the glare. In certain regions in the Sudan and Northern Nigeria, for instance, smoked glasses are a necessity to mitigate eye-strain. A proper sense of colour vision is essential. Chronic conjunctivitis of all kinds constitutes a distinct disability.

Middle-ear disease with discharge is a definite disqualification, as is also aural eczema: both are made worse by tropical conditions. Perforation of the tympanum and any kind of deafness must be investigated. Deafness in more than a moderate degree is a bar to acceptance.

Respiratory system.—Special attention must be paid to the lungs. Asthmatics and subjects of "hay fever" are quite unsuited

for tropical residence, as are those suffering from chronic bronchitis and also those with emphysema. Any suspicion of tuberculosis, whether glandular or parenchymatous, calls for X-ray examination. This specially applies to candidates having a bad family history.

The Editor is strongly of the opinion that any candidate having a Ghon's focus, or any evidence of healed apical lesions, is quite unfitted for the tropics. Contrary to popular opinion, damp heat induces, fosters, but does not cure tuberculosis. Those who have calcified bronchial glands, and who have already demonstrated thereby their resistance to the disease, may on the other hand, be considered suitable.

Cardiovascular system.—Any valvular heart disease is a contra-indication. It is probably true that persons with mild degrees of mitral stenosis are not seriously inconvenienced by tropical life, but the increase in the metabolic rate and the strain placed upon the heart and respiratory organs by extreme heat has a deleterious effect upon the action of the heart. Of all heart lesions, *aortic regurgitation*, especially when of luetic origin, constitutes a definite disqualification. Sinus arrythmia and extrasystoles are frequently encountered in tropical residents, and are not in themselves deleterious. Persistent tachycardia, from whatever cause, should be a bar to tropical service, and a candidate exhibiting a rapid pulse, which does not arise from nervousness during the medical examination, should be subjected to a searching exercise tolerance test.

Hyperpiesia.—Subjects of high blood-pressure are definitely excluded. Hyperpiesia, due to intrinsic hypertension or arterio-sclerosis, is a serious handicap in the tropics. Often, in nervous young men a high systolic reading may be obtained, and while this for the most part can be overlooked, a persistent high diastolic pressure above 100 mm. Hg is a definite disqualification. Such persons inevitably break down after prolonged tropical residence ; they are more liable to develop neurasthenic symptoms, and, in the Editor's experience, usually end up with cerebral hæmorrhage.

Digestive system.—In investigating the antecedents of the candidate for service in the tropics nothing is more important than his " digestive " history. The organs of digestion are necessarily subjected to considerable strain ; therefore subjects of nervous dyspepsia, hyperchlorhydria, or severe gastric disturbances, should not go abroad. A previous history of duodenal or gastric ulcer, especially where definitely confirmed by radioscopy, should debar a candidate, especially from places characterized by damp heat, such as is encountered on the west coast of Africa, or in Malaya. It must be remembered always that, even under the best circumstances, a great deal of the daily fare will consist of frozen or tinned food.

If the indigestion is due to chronic inflammation of the *appendix*, it is most important that appendicectomy be performed prior to sailing. It is obvious that for many reasons, " appendicitis " is a much more

dramatic and important occurrence than it may be in more highly civilized conditions.

Persons of a "bilious" or a hepatic tendency, with lustreless skin and a jaundiced look, withstand the tropics badly; therefore any palpable enlargement of the *liver* must be noted. *Splenomegaly* may, occasionally, denote previous attacks of malaria, and it may indicate that the candidate is hypersensitive to this infection or, on the other hand, it may mean that he is the subject of some obscure blood disease, and is therefore unsuitable.

Sufferers from chronic colitis are ruled out. A history is not always easy to obtain; but if there is any previous history of passing either blood or mucus in the stools, or both, or pain on defæcation, or any suspicion of ulcerative colitis, the matter must be investigated. This disease is so liable to remissions that the candidate may appear well and healthy at the time of examination, but relapses under tropical conditions are apt to be specially severe. The peculiarly sensitive type of persons who are colon-minded, and are subject to mucous colitis and spastic colon, thrive badly and cannot be recommended. Subjects of diverticulitis fare badly, also, and if this condition is detected as a cause of abdominal discomfort in a more elderly subject, tropical service is not recommended. Any history of gall-bladder disease should debar the candidate, owing to the risk of cholecystitis and biliary calculus developing under tropical conditions.

Hæmorrhoids.—Piles are a curse of life in hot climates and under these conditions persons predisposed to the disorder almost invariably become sufferers. Piles should be removed surgically, as injection methods do not appear to be altogether satisfactory.

Hernia.—Candidates with inguinal herniæ of any description must submit to operation before going abroad. Trusses, even of the lightest variety (celluloid), are most inconvenient, and in the tropics are apt to cause intertrigo and skin irritation. The same applies to umbilical herniæ. Pads cannot be worn and are usually inefficient.

Genito-urinary system.—Renal and vesical calculi are more likely to develop in the tropics than in temperate regions. No one with a previous history of renal colic should be accepted. Enlarged and palpable kidneys may mean congenital cystic disease, and constitute a definite disqualification. Special attention must be paid to the examination of the urine. Moderate degrees of albuminuria (physiological or postural) are extremely common in athletic and otherwise healthy young men, and the Editor is of the opinion that it is quite unfair to reject a suitable candidate merely on this account. In cases in which there is really an appreciable amount of albumin (5 per cent.) the matter assumes a different aspect. The presence of casts in numbers in the deposit indicate a predisposition to severe renal disease. The discovery of sugar in the urine, however, is a somewhat different matter. If a very considerable precipitate is obtained with Fehling's and Benedict's solutions, then a blood-sugar curve estimation must be done. No

diabetic ought to be passed for service in the tropics. Opinions vary about renal glycosuria. If the candidate has a low sugar tolerance with a low renal threshold for glucose, he is best out of the tropics, as the condition may possibly predispose to true diabetes.

The cellular deposits of the urine should always be examined. Subjects of phosphaturia, so-called "*phosphatic diabetes,*" owing to the concentration of urine which occurs in a hot climate, are unsuitable. Those showing evidence in the urine of Bacillus coli, or streptococcal infection, must be rejected. A constant source of trouble is urinary tuberculosis, on account of the difficulty of detecting the tubercle bacillus; but in cases in which large numbers of pus cells are present in the urinary deposit without other ascertainable cause, the possibility of tuberculosis should be suspected and the candidate rejected. Chronic gonorrhœa and chronic prostatitis are always a source of trouble and constitute a reason for rejection.

Female candidates.—Among women, disorders of the genital organs tend to dominate the picture. Since impairment of the menstrual functions is usually aggravated by tropical residence, the menstrual history must be carefully investigated. Those inclined to dysmenorrhœa, or menorrhagia, should be forbidden, if possible, to go out. Subjects of periodic amenorrhœa suffer more in the tropics, and the same may be said of women who suffer from uterine displacements. Women who are married and predisposed to miscarriage are more liable to this accident under the less civilized conditions of the tropics.

Minor vaginal or uterine disabilities, such as vaginal discharges, may be overlooked. Women in advanced pregnancy should not attempt to go out, and it is advisable that a primipara should not proceed to a hot climate in the middle of her pregnancy.

Integuments.—Special attention must be paid to the skin, hair and nails. *Alopecia* is more apt to progress under tropical conditions. *Cracked* and *brittle nails* indicate a feeble constitution. *Clubbed fingers* may indicate cardio-pulmonary disease, or may be merely a congenital deformity. Anyone with an abnormal *skin* must be specially investigated. It must always be borne in mind that the skin, as an organ of elimination and metabolism, is a much more important organ of the body in tropical than in temperate countries. There are subjects of deficient sweating (anidrosis); such persons, unable to sweat freely, not only suffer acute discomfort but are in unnecessary danger from heat stroke and heat exhaustion. Therefore candidates having dry skins (xeroderma) and ichthyosis, must be rejected. On the other hand, individuals whose sweat-glands are abnormally active do well.

Septic spots on the skin of the back and chest are frequently encountered in young men, and though each case should be judged on its merits, it should be remembered that residents in most tropical countries, but especially in West Africa, are particularly prone to septic infections, especially boils, so that anyone who is specially susceptible to the staphylococcus should be considered unsuitable.

Subjects of *psoriasis* are always a difficulty. Milder degrees may be passed over, and as a general rule these lesions are apt to disappear in very hot countries. Extensive psoriasis, however, especially when associated with suppuration, should debar from the tropics.

Acne.—Acne is one of the skin diseases which are improved by heat, and as many healthy and vigorous individuals are marred by this complaint, they should be permitted to proceed.

Eczema of all kinds is a distinct disability and so are sensitive (allergic) skins, and those prone to intertrigo.

Central nervous system.—It has already been sufficiently stressed that nervous control is of paramount importance in the tropics. All exhibiting neurotic and hysterical tendencies should be rejected. *Epilepsy* is not always easy to detect; epileptics must on no account go to the tropics. Any chronic affection of the spinal cord, e.g., Friedreich's ataxia, or spastic paraplegia, is a disqualification, as is a previous history of encephalitis lethargica, or of cerebro-spinal meningitis.

A candidate sometimes appears who has suffered in the past from infantile paralysis. If it merely affects one limb, and the muscular atrophy is not too extreme, he may be passed, though it must be understood that the tropics is no place for a cripple. Exaggerated deep reflexes and tremors of hands, or tongue, denote that the candidate has an unstable nervous control, and that he is unsuitable.

GENERAL DISEASES AND DISABILITIES

Anæmia.—Persons with anæmia which cannot be adequately explained are usually in poor health; they are what is rather indefinitely described as "below par," and this succinctly suggests that they are lacking in vigour, energy and initiative. The pale young man or the sallow woman is unsuited for tropical residence. The hæmoglobin content is probably of more importance from this point of view than the red-cell count. Secondary anæmia is usually indicative of some underlying condition. It may be digestive in origin; it may be pulmonary, or even cardiac. Pale faces become still paler in the tropics, and the condition is more likely to progress there.

Affections of the thyroid.—The possibility of hyperactivity, or of insufficiency of the thyroid gland, has to be kept in mind. The Editor is convinced that all thyroid tumours, whether adenomata, cystic adenomata, or just plain thyroid hypertrophy, are definite contra-indications to tropical service. The form of hyperthyroidism (usually due to substernal thyroid) which, though not leading to exophthalmic goitre, yet produces thyrotoxicosis with a special brunt upon the cardiac muscle, is specially to be feared. The thyrotoxic heart is produced by exposure to tropical conditions, and may progress

unchecked and end fatally. All degrees of hypothyroidism are also unsuited to tropical conditions.

Other endocrine disorders.—Endocrine disorders, such as hyperpituitarism, hypopituitarism, "Fröhlich's syndrome," achondroplasia, and developmental anomalies, are definitely to be excluded. Giants and dwarfs, even if perfectly naturally developed and proportioned, are not to be recommended, not so much for physical unsuitability, as from psychological grounds of undesirability.

Gout and rheumatic arthritis.—A gouty diathesis is occasionally seen in comparatively young people, and may manifest itself in many ways. Gout may actually be provoked or aggravated by tropical conditions, and therefore must be regarded as a contra-indication. There is a popular idea that rheumatic affections of the joints are improved by exposure to heat, but this is far from being the truth. Usually, far from being relieved, such disabilities are aggravated. The same is true of fibrositis.

Other disabilities.—Even such minor blemishes as the state of the feet must be inquired into. Such conditions as deformities, club foot and hammer toes, in those who may be called upon to undertake long marches, may be held to be distinct disabilities.

Preparations before sailing.—All those who are proceeding to the tropics and subtropics, whenever they come into contact with native servants, and whenever they mix with the native population, or whenever they are forced to live in less sanitary surroundings than they have been accustomed to, should be inoculated about four weeks prior to departure against typhoid and paratyphoid (T.A.B.) (*see* p. 343). They should also be revaccinated, if this has not been done within the three previous years. Very often this vaccination may not cause any obvious reaction, or in popular language, may not "*take,*" but it must be attempted none the less. The vaccination may be conveniently performed at the same time as the second inoculation. If for other reasons, such as business matters or preparing for departure, circumstances prevent this being done, both inoculation and vaccination can be undertaken on board ship if the voyage is of sufficient duration, e.g., the journey to India. Allowance must be made for any possible reaction. Thereafter it should be the rule to repeat the vaccination every five years, and the inoculations at three-year intervals. Those proceeding to the West Coast of Africa, other parts of the Dark Continent and South America, where yellow fever is endemic, are nowadays strongly urged to be inoculated against this disease (*see* p. 375). It must be emphasized that out of the thousands who have now been protected not a single one has contracted yellow fever. A period of five weeks should elapse after the inoculation in order to permit recovery from any possible reaction, and the development of sufficient immunity before the voyage is undertaken. The minimum period should be three weeks.

There are some persons who exhibit an idiosyncrasy to quinine,

and it is advisable, in the case of persons going to regions where quinine prophylaxis is practised, that they accustom themselves to the action of this drug by taking a trial course on board ship.

ON PASSING PATIENTS AS FIT TO RETURN TO THE TROPICS ON EXPIRY OF THEIR LEAVE

Special care should be taken over the "passing-out" examination prior to return to duty from leave. This specially applies to those who have suffered from nervous debility, with attendant insomnia and associated psychological disturbances. In these cases a full period of leave must be granted for recuperation. The mind must be serene, the reflexes normal, and the patient should eagerly anticipate his return, and not *recoil* from the very idea. Those who have had malaria should have fully recovered from the infection; the spleen should no longer be palpable, and the blood should reach the normal standard. Should blackwater fever have supervened, and should it be an isolated attack, and recovery be complete, the patient may be permitted to return; but if he has suffered from more than one attack and has survived, it is extremely dangerous to risk a third (*see* p. 105).

Other tropical blood infections are trypanosomiasis and kala-azar. Both of these, formerly so greatly feared, are now amenable to treatment and cure by means of specific drugs, and the cure is so dramatic and complete that in cases of these infections, provided there has been a suitable period for convalescence, no valid objection can be urged against a return to duty.

Relapsing-fever cases are generally completely cured of their infection on arrival in this country, and if no disability remains they are suitable for return. There are the tropical typhus and undulant groups, victims of which are seen comparatively commonly: in both of these recovery is generally quite complete, and no physical disability remains. In the latter group, however, a sufficient period of leave must be granted for full convalescence.

Other tropical infections to which special attention should be given belong to the dysenteric group. Amœbiasis was formerly the subject of considerable apprehension, because of the absence of a final test regarding its ultimate cure. It is true that incompletely cured patients, and those who continue to harbour cysts in their stools, are more liable to relapse under tropical conditions than those who continue to reside in temperate climates. Therefore, all those who have suffered from clinical dysentery during their period of service should be specially examined on their return. Their stools should be examined for amœbic cysts, and a sigmoidoscopic examination performed, if necessary. There is no objection whatever to the return of dysenteric patients, provided they have undergone a thorough course of anti-amœbic treatment. Those who have suffered from bacillary dysentery, on the other hand, and they are much more numerous than is generally

thought, usually make a complete recovery on return to England, and relapses are not to be anticipated. The form known as chronic bacillary dysentery is much more refractory, and it is doubtful whether in these cases the patient recovers sufficiently to return.

Another important form of tropical diarrhœa is sprue (*see* p. 570). There is always considerable hesitation in permitting these patients to return to the tropics, especially to the locality where the disease was first contracted. It is undoubtedly true that relapses are more liable to recur in the tropics. Probably complete recovery occurs in comparatively young people under forty years of age, and if they have been quite free from all symptoms and signs for one year at least, then a return to the tropics may be sanctioned.

Ancylostomiasis and other worm infections are not infrequently the cause of loss of vigour and ill-health in those returning from leave. The possibility of an ancylostome infection must always be borne in mind as the cause of cachexia and fatiguability, especially in women who have been residing on tea estates and other plantations. Their stools must be examined by concentration methods with this point in view (*see* p. 1031). After adequate treatment they are fit to return.

Postoperative Debility

The question as to when a patient is to return subsequent to operation is always a debatable point, especially in cases of operation on the gastro-intestinal tract. Appendicectomy, and even cholecystectomy, are quite simple and give rise to little difficulty, but in the case of more elaborate operations, such as gastro-enterostomy for duodenal ulcer or pyloric stenosis, circumspection is called for. The Editor is very chary of permitting such patients to return to tropical conditions where circumstances are adverse, unless the operation has been a distinct success, the patient's condition excellent, and his digestion perfect.

The same general rule should be applied to operations on the genito-urinary tract. Renal calculi are common in the tropics, and certain individuals seem predisposed towards this condition. If nephrectomy for renal calculus has been performed, and the patient is in a good state with one functioning kidney, there is no objection to return to the tropics, provided that it is not to a hyperendemic malarial zone. To a person with one kidney, an attack of malaria or blackwater fever may become a matter of life and death.

ACCLIMATIZATION

It is obvious that the effect of transportation to the tropics, where the isotherm may be anything from 20–30° F. above that previously experienced, is to subject the body to considerable strain and to consequent alterations in metabolism. It is also a matter of common knowledge that individuals vary to a very great degree in their re-

actions to heat. There are those who suffer greatly during a spell of hot weather in England, a so-called "heat wave," under conditions which are about the average in any region between Capricorn and Cancer, so that it is by no means easy, in the present state of knowledge, to assess these individual variations.

The saying "What is one man's meat is another man's poison" also applies to climate; but instinctive dread of extreme degrees of heat and humidity is rapidly diminishing as communications are being opened up by air travel. The aeroplane, the motor car and the refrigerator have robbed many places of most of their terrors, and the West Coast of Africa is no longer the White Man's Grave. It is common knowledge that some individuals, who as likely as not are of indifferent physique, thrive in the tropics; there are some, for instance, who prefer to live in Central Africa, though these are quite exceptional.

Within a relatively short space of time we have seen arise a full-blooded European tropical population. In the British Empire there are such communities in India, Ceylon, Burma, Queensland, and the highlands of Kenya. It may therefore be asked: Can the European preserve his identity, maintain his vigour, energy and culture; can he in fact hold on to whatever is held dear in European civilization under the stress of tropical conditions? The answer is hard to supply and in recent years has become bound up most conspicuously and intimately with the "White Australia problem."

Many striking examples of adaptation could be quoted. Thus Gorgas has cited the large-scale experiment of Panama, where for ten years Americans, including men, women and children, mostly doing hard manual labour, exposed to all kinds of weather conditions, remained in good health. The European inhabitants of the West Indies, Barbados, Jamaica, St. Kitt's, Antigua and the islands of St. Martin and Curaçao, are the descendants of white settlers and are to be found to-day, healthy and vigorous. The German colony of Espirito Santo, in Brazil, which was founded in 1847, is now in a flourishing condition, with a birth- and death-rate comparable with that of Europe.

There is also the oft-quoted unintentional experiment which took place in the Dutch East Indies 274 years ago. In 1665, eight Dutch soldiers were sent by the Netherlands East India Company to the little island of Kissa, 16 miles off Timor. It appears that this lonely outpost was quite forgotten, and the men soon realized that they had been marooned. They had their wives with them, so they built houses and cultivated the land. They have been wonderfully fertile and now number over 300, and are a sturdy race, with no signs of ill-effects from inbreeding. Many have European fair faces and complexions, and many of the children have light hair and blue eyes. The example of the Dutch Island of Saba is also quoted by Bagshawe. This lies near St. Kitt's and, for 250 years, an English-speaking white community, without racial admixture, has existed and multiplied, though it is now

declining under the stress of economic circumstances. Price, in 1934, in writing of this community, concludes that cold-temperate zone whites can retain a fair standard for generations in the trade-wind tropics, provided that the location is free from the worst forms of tropical disease, and that the economic return is adequate. Whatever may be the ultimate truth of this matter, it is not only advisable, it is necessary, to send European children, at six or seven years of age, back to a temperate climate to be educated. With few exceptions, serious harm results from keeping white children too long in the tropics, though European infants up to four or five years, it is true, thrive in most tropical climates with the exception of the West Coast of Africa.

After prolonged residence in tropical highlands, especially those of East Africa, neurasthenic changes are specially liable to develop; if not in the first, then, more certainly, in the second and subsequent generations. While exceptional examples of the survival of the European race in some tropical, though mainly insular climates, exist, the general consensus of opinion is to the effect that the white man cannot long survive or multiply in a pure state in most tropical countries.

TROPICAL CLIMATES

According to Supan's classification the following are the main types of climate :—

Tropical or warm climates.—Tropical climates extend from the equator to the mean annual isotherm of 20° C. The northern limit is situated at 35° of north latitude; the southern at rather less than 30° southern latitude. The true tropical zone is divided from the subtropical by a purely arbitrary line which represents the isotherm of 20° C. for the *colder months* of the year in both northern and southern latitudes. The tropical zone corresponds more or less to 23½° N. and S. latitude, being more or less confined to the tropics of Cancer and Capricorn.

The *subtropical zone* lies between the isotherm of 20° C. (68° F.) for the temperature of the coldest month, and the same for the mean temperature of the year. This includes a portion of North America and a considerable portion of South America, Africa, Asia Minor, Iran, North India, China and Australia.

In the tropics there are four divisions of warm climates, viz., the equatorial, the trade-wind, the monsoon belt and the mountain climates.

The equatorial belt.—Those localities within a few degrees of the equator are always subject to rain and cloud, because the hot air is charged with aqueous vapour from the sea. This belt is subject to alternate seasons of wind and calm, e.g., in January to the north-east trade winds, and in July to the south-east trades. Such places are Southern India, Ceylon and Java, Colombia, South America, parts of the Nile Valley, and the Gold Coast.

Trade-wind belts.—The lands which lie outside the boundaries of the equatorial or rain belt, situated some 20° to 35° N. or S. latitude, are among the driest of the world, except in India, where the south-west monsoon brings a little rain into the dry regions of the Punjab and Sind. These places are the dry zones of California, and other parts of North America, the Sahara

and Nubian Deserts, parts of Arabia and Iran, Argentine, South-West Africa and the interior of Australia.

Monsoon belts.—The monsoons are classifiable into:—North-east, south-west, north-west, south-east, and west monsoons.

The *north-east* and *south-west* monsoons are met with in the Indian Ocean and on its coasts. The interval between these two monsoons is characterized by changeable winds, which blow alternately in opposite directions—north-east and south-west. The latter prevails in May, June, July and August; the north-east, which is due to the cooling of the plains, is really a trade wind, and blows in November, December, January, February and March. On the south-west monsoon southern India largely depends for rain.

North-west and south-east monsoons are to be found in the southern hemisphere, especially in Australia.

The *west monsoon* is a wind which blows in a south-westerly direction, along the coast of Africa, from the Cape Verde islands down to Walfisch Bay.

Climates.—The effect of elevation is to lower the temperature. This is due partly to the expansion of the air, partly due to the lessened amount of earth to radiate *black heat* (or that which is absorbed by the rocks and soil), and partly to the movement of the wind.

The greatest blessing of these elevations in the tropics is that they provide cool hill stations to which resort may be had during the hottest months, and where the climate simulates perpetual spring.

The main factor in tropical climates is the sun's rays, which are vertical and thus penetrate to a degree unknown in temperate zones; at the zenith they are fifteen times stronger than when the sun stands 10° above the horizon. There are two other climatic factors which act adversely; these are the humidity of the air, which is usually much higher than any experienced in Europe, and the air currents. Apart from these the main disturbing factor to the newcomer is the small daily variation in the temperature, which seldom falls below 68° F.; in vain he longs for the coolness of the twilight. The very evenness of the tropical climate, so different from the extremes in which the European has been brought up, does not lead to alleviation of existence, but to the very opposite. The lack of daily variations between night and day, winter and summer, become monotonous and devoid of the stimulus to which the European has been accustomed, and this is paralleled by the everlasting twelve hours of darkness succeeded by twelve hours of light. The low-lying tropics usually have an isotherm of 78° F. compared with that of Central Europe of 48° F., but for every 300 feet of elevation above sea-level the temperature is reduced by 1° F.

It must not be thought that the geographical demarcation of the torrid zone necessarily embraces all the true tropics; this is by no means the case. As regards actual heat, the highest isotherm lies some 10° north of the geographical equator, and north and south of this line is an isotherm of 20° C. (68° F.), and even within this warm zone there is a subdivision where, in the cooler months, the temperature never falls below 68° F.

Three factors must be considered in any tropical climates; these are the humidity of the air (the wet-bulb temperature), which usually reaches a figure of over 80–90 per cent.; the actual temperature; and the air currents. Thus it comes about that it is not right to speak of a "tropical climate" as a complete entity, as there are minor variations to be found within the tropics themselves. We can recognize within the tropics every intergradation between a marine and a continental climate, and even with very considerable

seasonal variations on tropical seaboards and in tropical islands. Thus, in the Antilles and in the Pacific variations of 30° F. are the rule, whilst inland, in the centre of the African continent, these variations may be as high as 64° F. Naturally, the amount of rainfall and the duration of the season exert a considerable influence upon the temperature and the humidity.

In India, the Far East and other parts of the tropics, the rainy season is known as the *monsoon*, so that there are considerable temperature variations during the dry and wet seasons.

In the northern summer, portions of the Asiatic continent become overheated, and in the southern summer the Australian and African continents become influenced in like manner, and thereby air currents are initiated, which are known as the south-west monsoons of India and East Africa, the north-west monsoons of Australia, and the north-east monsoons of East Africa; and in the regions lying between these there are minor intergradations of these major winds.

The summer monsoons are invariably sea winds, which bring rain and overcast cloudy weather, and if they blow from a cooling sea, cause a drop in temperature. The winter monsoons, on the other hand, are land winds, and are accompanied by hot, dry weather and a rise of the temperature; the relative dryness is determined by the character of the continent from which they come. Sea currents to a certain extent influence tropical climates.

Thus the cold antarctic current does considerably cool off the air on the west coast of South America, where the coastline comes into contact with the Antarctic or Humbold current, and this exerts a considerable effect upon the rainfall, which may be, as in Chile and Peru, practically non-existent. The barometer pressure is, on the average, considerably lower than in temperate zones, but its influence upon human well-being is not understood.

The regulation of heat.—A given area of a portion of the tropics receives the same number of rays from the sun as any other place on a line drawn round the globe in the same latitude, but atmospheric heat is not derived directly from the sun's rays so much as from the *black heat* which is radiated from the land and sea. The rays from the sun heat the earth first, the process being known as *insolation*. This heat has little power on land and its effect is sensibly diminished even twenty feet above the surface of the earth. The earth is surrounded by a gas envelope, or *atmosphere*, the density of which is equal to a pressure at sea-level of 15 lb. to the square inch, becoming less dense the farther we get away from that level. This atmosphere absorbs a large proportion of the sun's rays which strike its outer limit; hence the sun's rays, which travel obliquely in the temperate zone, traverse a thicker layer than the rays which travel *vertically* in the tropics. In this way in the non-tropical regions radiation is absorbed by the intervening atmosphere and the power of the sun correspondingly diminished.

PHYSIOLOGICAL EFFECTS OF A HOT CLIMATE

Observations have been made on the effects of tropical climates on body temperature, skin reaction, respiratory exchange, urinary excretion and the blood, with conclusions on the influence upon digestion, circulation, nervous system, generative organs and growth.

On body temperature.—On passing from a temperate to a tropical climate, a slight rise in body temperature occurs, rarely exceeding

1·5° F., and after arrival in the tropics the body temperature of the newcomer remains slightly elevated. In fully acclimatized Europeans it settles down to normal, but tends to rise after severe exercise. Breinl found the rectal temperature to be 101° F. (38.3° C.) on really hot days.

Low fever.—Low fever is the term given to a little understood clinical picture, and it is by this vague description that it is known all over the world. It is characterized by lassitude and debility, and a long-drawn-out slight rise of temperature, which is frequently seen in children. Very little has been written about this condition in text-books, but all are agreed that, in spite of the most searching bacteriological and biochemical tests, no specific organism can be held responsible. If low fever cannot be assigned to latent malaria, amœbiasis, closed tuberculosis or gonorrhœal prostatitis, then it is certainly due to climatic causes, and probably " climatic fever " would be a better term. It occurs in particularly thermotropic individuals who have come to the tropics with a sensitive nervous system, and are reacting to the climate, either temporarily or permanently, with a slight rise of temperature. In these cases the temperature seldom rises above 100° F. at the hottest period of the day; but the most noticeable feature is that the daily minimum is raised the same amount as the maximum. *The daily variations remain the same as before, but the entire level is shifted upwards.* Some of these patients feel chilly at times, and during these spells are most uncomfortable. Occasionally, too, there are spells of excessive sweating.

Skin reaction.—The regulation of body temperature is effected by evaporation of water from the surface of the body and from the lungs. It has been shown that on a white skin, with the appearance of perspiration the temperature falls, and the greater the degree of perspiration the greater the fall of temperature. A brown or black skin absorbs more heat than the white skin, and the point where perspiration shows itself is reached earlier in the case of the brown-skinned, showing that his cutaneous heat-regulating apparatus is more sensitive than that of the white man.

On respiratory exchange.—The cooling process is brought about by evaporation of water from the lungs. This is also to some extent effected by the attraction of the blood to the surface of the body. The place of the blood thus transposed is taken by air, and this is one of the reasons why the lungs weigh less in hot than in cold or temperate climates. The lung capacity is increased, and thereby the respiratory rate lowered; this results in the inspiration of less oxygen, and consequently less carbonic acid and water vapour are given off by the lungs. One of the results is retention of carbon dioxide in the blood.

On urinary excretion.—The excretion of urine is, with excessive sweating, diminished. The daily output of a normal adult in the tropics is 500–600 c.c. as against 1,500 c.c. in temperate countries. The urine

is concentrated, but apparently contains the same amount of waste material as that found in 1,500 c.c.

On the blood.—*Apparently, as the result of investigations made* in Java, the Philippines, Queensland, West Africa and Iraq, climate alone produces no change in the formed blood elements, except a shift of the Arneth index to the left (*see* p. 1025). Nor does it produce any change in the hæmoglobin content, or the specific gravity, of the blood. De Langen and Schut in Java asserted that in the newly-arrived European the blood sugar is augmented; or, at any rate, there is a rise in the fasting level. On the other hand, Sundstroem concluded that the endocrine glands in the tropics exhibit a decrease of functional activity and that, therefore, a parallel decrease in blood sugar should take place. He found that this actually obtained in European individuals of both sexes who had lived in the tropics since birth. A positive correlation, moreover, was found to hold between the sugar values and the lecithin and cholesterol ratios of the blood.

The non-protein nitrogen, on the other hand, was about 25 per cent. higher than the standard average, but the urea, uric acid and total creatinin failed to disclose any abnormalities. It is thought that endogenous and exogenous toxic substances, usually excreted by the kidneys, may be subjected to retention and possibly predispose to the greater susceptibility to nephritis in a tropical climate. The liquid phosphorus content of the whole blood was found by Sundstroem to be normal in individuals who had spent less than one year in the tropics, after which a drop was noticeable down to 9 mgm. per 100 c.c. for men, and to 7 mgm. for women. Various suppositions are advanced to explain the diminution of blood phosphorus in the tropics. It is thought that a climatic stimulus may temporarily throw an excessive load on the mechanisms which supply phosphorized material for anabolic processes. The content of total fatty acids in the blood of tropical residents appears to be considerably lower than the available standard figures for cooler climates, and this is thought by de Langen to explain the rarity of gall-stones in Malays and Javanese. As a general rule, the blood becomes more concentrated in a hot environment, and the chlorides of the blood occupy a consistently higher level in the tropics than that in cooler regions, and thereby indicate an augmented water intake.

On the digestion.—At first, as every traveller will testify from experience, there is a stimulation of appetite, as well as of the digestive function, but this is a passing phase, and is soon replaced by a diminution of appetite and a lowering of the digestive capacity, together with a diminished desire for animal food. Diarrhœa and loose stools are almost invariable on first exposure to tropical conditions, and are soon followed by constipation.

On the circulation.—Exercise and humid heat produce a rise in blood-pressure, and also in the pulse-rate (Breinl). The average systolic blood-pressure shows a tendency to fall concomitantly with

profuse sweating. The diastolic pressure follows closely the course of the systolic.

On the nervous system.—On the nervous system, the first effects are of those of stimulation, followed by depression, and when the latter is prolonged a neurasthenic state with loss of memory (" West Coast memory ") is produced. In tropical residents of long standing there is an exaggeration of the deep reflexes, tachycardia and, eventually, the production of insomnia and abnormal reaction to stimuli, which indicates a loss of control by the higher centres, and results often in unreasonable mental irritability. Electrical conditions also affect the nervous system powerfully. Among European children, especially, in the tropics the whole nervous system appears to be in a condition of unstable equilibrium, resulting in fretfulness and peevishness and often in frank hysteria.

On the generative functions.—In both sexes there is a stimulation at first of the sexual libido, but excess is soon followed by exhaustion, and often results in sexual neurasthenia. In children, puberty is attained at an earlier age, so that in European girls menstruation commences about a year earlier than in temperate climates, but the onset of the menopause at a later age is not affected.

On growth.—Growth in children is rapid, and is therefore associated with a corresponding loss of weight and physical strength. European children brought up in the tropics are generally described as " weedy."

Acid-base equilibrium and basal metabolism.—Sundstroem and Radsma are the only authorities who have carried out much work on these problems. The former finds that, as a rule, the alveolar carbon dioxide tension is lowered in the tropics. An alkalosis is present in the majority of tropical residents at the height of the hot season, and may have an undesirable effect upon their physical well-being. It is further suggested that an adequate water intake and muscular exercise may prove effective in combating this tropical alkalosis. The importance of disturbances of endocrine functions is emphasized in so far as energy metabolism is concerned. It was found by Sundstroem that the basal metabolism varied between 25·5 and 36·1 calories, with an average of 31. Variations in the dry- and wet-bulb temperatures may affect the level of basal metabolism in certain individuals. Radsma concludes that the basal metabolism in Europeans is reduced, or is, at least, lower than the standard values which obtain in Europe and America.

Perspiration.—Adaptation to high temperatures involves an increased capacity to produce sweat, a greater sensibility of the temperature regulatory apparatus, and an economy of salt. In failure, such as that due to excessive salt loss, or to a steadily rising temperature, the sweat glands may be at fault. Anyone who is exposed to high temperatures should take warning if a degree of exhaustion increases with each day of work, and if his degree of recovery decreases with each night of rest (Dill).

Sweat varies in composition, depending upon its rate of production.

In very hot weather, salt depletion is high, not only because of the large volume of sweat produced, but because this sweat is unusually high in salt content. Whilst the sweat glands excrete lactic acid, it is believed that this is not wholly dependent upon muscular exercise.

Thirst.—Thirst does not necessarily depend on a dry mouth, nor does it depend on the volume of blood plasma, nor of the extracellular phase of other tissues. It depends upon the diminished water content, and possibly upon increased osmotic pressure, of body cells. Whilst thirst may be somewhat alleviated by rinsing the mouth, it can be satisfied only when water has been delivered by the blood-stream to the tissue cells demanding it (Dill).

PATHOLOGICAL EFFECTS OF TROPICAL CLIMATE

The tropical light naturally produces effects in the skin which may be acute or chronic. They may range from a slight sunburn to a severe erythema, accompanied by blisters and œdema, and a severe reaction may set in, accompanied by œdema and septic absorption. Sometimes this may be so severe as to produce delirium, and even coma. Chronic skin irritation is shown by pigmentation and by vasomotor changes, and that this is a process of natural selection is demonstrated by the skin pigmentation of most native races, so that the nearer the equator, the darker the skin. The skin of a European long resident in the tropics tends to darken, but pigmentation does not necessarily take place. When slight pigmentation is established, probably as the result of increased blood supply, hair and nails grow more rapidly. Freckles—small brown pigmented macules—are specially liable to occur in the sandy, red-haired, or fair children brought up in a tropical climate, and are often very disfiguring. Chronic solar dermatitis, or sailor's skin, is characterized by atrophy, wrinkling, pigmentation, white atrophic patches, telangiectases and warty growths (solar keratoses), some of which, especially when situated on the dorsum of the hands, eventually become the seat of basal (rodent ulcer type) or squamous-celled neoplasms.

Summer eruption is a polymorphic eruption of erythema papules, vesicles, weeping areas, crusts, pigmented macules and small depressed scars, which occurs in exposed parts, especially among children.

Urticaria is occasionally produced by the actinic rays. *Xeroderma pigmentosum* (Kaposi's disease) is a congenital condition of light-sensitiveness, such as is produced by X-rays on a normal skin, and manifests itself by pigmentation, telangiectasis, keratoses, and finally epithelioma, and is produced by the ultra-violet region of the spectrum. It is said to be more frequent in the tropics than elsewhere. *The effect of tropical sunlight on the eyes* is well known to produce glare conjunctivitis, necessitating the wearing of smoked or tinted spectacles. Pterygium, or a triangular fibrous growth extending over the conjunctiva to the pupillary margin with its base towards one or other

canthus, is common in tropical residents, and is considered to be a natural reaction to intense sunlight.

The congestive disorders affecting especially the liver and bowels are probably due more to sudden changes of temperature. The concentration of the urine predisposes to gravel and probably accounts for the frequency of renal and vesical calculi in tropical residents, especially in hot dry climates, such as that of the plains of India and the arid districts of the Sudan and Northern Nigeria.

CHAPTER II

LIFE IN THE TROPICS—(*Continued*)

CLOTHING AND GENERAL HYGIENE

Tropical clothing must protect the person from solar rays while interfering as little as possible with evaporation of moisture from the body. The clothes should be light and loose, whilst the material which comes next to the skin should be non-absorbent and such as can be frequently washed.

The *sun helmet* (or topee) should be white or khaki and have a dark or green lining. It should not exceed 15 oz. in weight, and the brim, sloping downwards, should project horizontally from the head for at least 5 inches. A projection posteriorly is useful, and some recommend an aluminium flap. The helmet is known as a sola topee, and is made of pith. At higher altitudes the double Terai hat may be worn. To prevent glare, and to mitigate the effect of heat, as some believe that the ill-effects of the solar rays are exercised through the eyes, smoked or tinted glasses should be worn.

Clothing should above all be loose, especially around the neck and chest. The fabrics usually worn are white or light-coloured, and cotton is best, whilst the vest or undershirt should be of the aertex cellular type. A light flannel shirt is popular. Whenever washable trousers or shorts are not used light cotton or calico drawers should be worn for the sake of cleanliness and to prevent skin irritation. The flannel cholera belt should be worn over the abdomen at night, and during the night only. A kummerbund is worn by men in the evenings, and does away with the necessity of a waistcoat. Where a coat or tunic is not worn, a spinal pad of dark material is very useful, and a strip of cotton sewn inside the shirt answers the purpose very well. Experimental work in the Philippines has shown that white or khaki are the best colours for external clothing as regards the powers of reflecting heat. Khaki is preferable for thin clothing, and white drill is stiff and not well ventilated; tussore silk is better still, but expensive. Most experienced travellers agree that the lighter the clothing, the better it is. Shorts are universally worn by men and, once the skin of the knees has become habituated to the sun, have many advantages, the chief disadvantage being that they expose an extra skin area to mosquito bites. This, however, can be avoided by providing flaps which can be turned down under the puttee or legging. The provision of slits under the armpits in the case of shirts and tunics is advisable.

Boots call for careful selection and should be half a size larger than those worn in temperate climates, as the feet swell readily in the heat. Canvas is on the whole better than leather.

Women's clothing in the tropics.—As far as possible women's clothing should be made of fine, soft cambric, which may have to be changed two or three times daily to prevent prickly heat. It should consist of two parts, viz., chemise and drawers, so as to secure a double covering for the abdomen. A loosely-woven cotton gauze, or a mixture of cotton with silk or wool, is best. Cashmere stockings should be worn. A white umbrella, or parasol, lined with green, is almost a necessity.

Children's clothing in the tropics.—Children's garments should be soft, light and loose. In very hot weather cotton gauze is best for underclothing, as the sensitive skin is very prone to prickly heat. To prevent the uncovering of the body at night-time, and to avoid chills, pyjamas of one piece of thin flannel should be worn.

Exercise.—Regulated daily exercise in the open air is necessary for the preservation of health in most tropical countries. It aids the body to get rid of waste material by inducing increased respiration, and is a stimulus to digestion and defæcation. It is customary to take exercise in the early morning and late afternoon. It is a great mistake to overdo hard exercise such as tennis or squash in a tropical climate to the point where undue fatigue is produced. This is more likely to be a mistake of newcomers.

Horseback riding is the ideal form of exercise for the tropics on the adage that the " best thing for the inside of man is the outside of a horse." A warm bath or a rub down should always be indulged in on return from exercise.

Sleep and rest.—A sufficiency of unbroken sleep is essential as a protection against the ill-effects of the tropical climate, but unfortunately it is not always easy to obtain. In the hot stuffy nights of the Indian summer, and during the dust-storms of Central Africa, sleep becomes almost impossible, especially when it is necessary to use a mosquito-net, which impedes the circulation of the already stifling air. Therefore it is better to sleep in a mosquito-proof room, which permits the use of electric fans. The ideal solution is an air-conditioned bedroom.

In most very hot countries, the daily siesta is customary, and is best taken before the midday meal or, if this is impossible, an hour afterwards. An hour's rest is recommended, especially in the case of European women and children.

Food.—It is scarcely possible to lay down general principles, since individuals and races differ so greatly in their conception as to what constitutes an adequate dietary. There is little doubt that the normal digestive capacity is less in the tropics than in temperate countries. Large quantities of food are not well tolerated, though possibly this may to a certain extent be attributable to monotony. The dietary should consist of foods which produce a minimum of heat. Of the true essential constituents, fats and oils have the highest caloric value, hence the almost instinctive aversion on the part of Europeans to greasy and fatty foods in a hot climate. There is usually, also, a distaste for animal food, a fact which, to a certain extent, is explained by the poor quality of meat obtainable and the lack of variety in cooking methods, but it is true that excessive meat-eating is harmful, unless the body is being actively exercised, probably due to incomplete digestion with the production of unabsorbed peptones, albumoses and hexone bases giving rise to the condition known as intestinal toxæmia. This is true for most tropical countries which have a cool season, such as the Sudan or Iraq. Meat can safely be eaten in the cold weather.

Generally speaking, the indigenous products of tropical countries are more suitable for food than any which can be imported. Sugar is a very valuable constituent of the diet in the tropics, especially for Europeans on the march, or on *safari*. Preserved dates and figs therefore have acquired a reputation among travellers, and it is wonderful how sustaining they prove, provided that the requisite quantity of liquid can be procured at the same time.

Breast-fed infants thrive as a rule, and it is said that the *quality* of the milk of European mothers is usually not impaired by tropical conditions. Most women, however, cannot stand the strain of nursing their own babies for any length of time. In Panama it has been found that the average milk of the coloured woman fosterer is richer than that of the European, and often upsets the digestion of the child, and in most parts of the tropics resort has to be made to artificial feeding. Cows' milk being very rarely obtainable, it is necessary to turn to various prepared foods, such as Mellin's, or to condensed milk. "Banana flour" is recommended as an excellent food for infants.

Beverages.—An ample supply of water is vitally necessary, and the amount varies according to the climate. During the hot weather in the Deccan in India, where the percentage of moisture is very low, it was found by Hunt that Europeans who lived in tents, and took a good deal of exercise, required no less than three gallons of water per head per day. This was also recognized during the Great War, in Iraq, where it was laid down that even a greater quantity than this might be needed under the conditions that prevailed there. Even with this supply it was found that the excretion of urine was by no means excessive. It has been pointed out that as much as 1·32 gallons are required to neutralize the heat produced by metabolism, quite apart from the heat added to the body by radiation and conduction. This holds for dry climates, with a high dry-bulb temperature, but in still, moist atmospheres, where evaporation is at a minimum, the imbibing of large quantities of fluid merely increases the discomfort.

Alcohol.—Widely differing opinions are expressed upon the subject of alcohol. By some—and it may be said the great majority—it is deemed a necessity and consequently beneficial, whereas by others, except in the case of the old and infirm, it is regarded as a luxury and held to be superfluous. Be that as it may, a moderate amount of stimulant, reserved as a "sundowner," probably does no harm, reviving the flagging energy and lending some colour to an otherwise monotonous day. It is probable that the average healthy adult male can deal satisfactorily with $1\frac{1}{2}$ oz. of alcohol daily, and in this connection, it is to be remembered that a beverage such as beer serves as a food as well as a mere drink.

Alcohol taken with the evening meal promotes good fellowship, stimulates the appetite and aids digestion, but the idea of the inevitable whisky and soda between meals is to be discouraged. It is time someone protested against the prevalent idea, fostered by the films, which insists on depicting the average Englishman in the tropics as imbibing a strong whisky with every sentence he utters. The implication is entirely false and, albeit, a libel on the race.

Aerated drinks are universal, and are useful in aiding digestion. The advent of the "Frigidaire," which, by providing cooling drinks which are beneficial in relatively small quantities, has done a great deal towards the comfort of life and the promotion of health in tropical countries.

PRINCIPLES FOR INCREASING BODILY COMFORT IN THE TROPICS

In order to maintain reasonable health in the tropics, and also to preserve working efficiency, it is necessary to improve the measures for promoting bodily comfort by every practical method. Human comfort in hot climates depends upon four factors : (1) The dry-bulb temperature, (2) relative and absolute humidity, (3) air movement, and (4) radiation to and from the surroundings.

When considering this problem it is essential to remember that the average individual is continuously producing 400 British thermal units of heat energy per hour within his body, due to chemical changes associated with circulation, respiration and glandular activity, so that it has been estimated that the resting human body produces, every hour, enough heat to boil a quart of water. It has been shown by direct measurement of the heat loss from the human body of normally clothed individuals sitting in an ordinary room in still air, at a temperature of 59° F. and 50 per cent. relative humidity, that the body loses heat to its environment in the following proportions : 45 per cent. by radiation ; 31 per cent. by convection and conduction to the air ; and 24 per cent. by evaporation by the moisture given out from the lungs and skin.

Although the mechanism for regulating the temperature of the body may increase the heat loss by sweating, if that heat loss is limited by the environment, considerable discomfort to the individual is produced. If the temperature of the walls of a room is 79° F. (in place of 59° F. already mentioned), the loss by radiation from the body is already halved. Radiation is increased by artificial methods for promoting currents of air, e.g., by electric fans, and the temperature of the air may be reduced by air-conditioning. These, however, and especially the latter, are expensive measures only to be undertaken in the larger and well-established centres. Air-conditioning in work-rooms and bedrooms is the ideal policy and this is now to be found in most tropical towns, but the expense of maintenance renders such means impracticable, save for large commercial undertakings.

With the idea of counteracting the radiant heat from the sun and sun-heated surfaces, Crowden has investigated the physical properties of low emissivity and high reflectivity for radiant heat possessed by bright metallic materials, such as aluminium foil. It has been shown by laboratory tests that by providing sun-helmets with an inside lining of bright metallic foil the heat radiated to the head is much reduced.

It has been found, too, that the insertion of a layer of aluminium foil in the walls of sheds and lightly-constructed buildings is highly effective. The provision of a one-inch air space and its replacement by reinforced aluminium foil adherent to thick kraft paper, affords insulation approximately equivalent to thirteen inches of brick. The

crumpling of the aluminium foil, so as to make it fully occupy the air space, appears to enhance the effect.

Preparations of aluminium and aluminium paint can be applied to the inside lining of tents and marquees, and this is a practical measure which is receiving considerable application for reducing the inside heat produced by radiation. Asbestos paper and cork lining, one inch thick, are also efficient, though expensive, insulating materials.

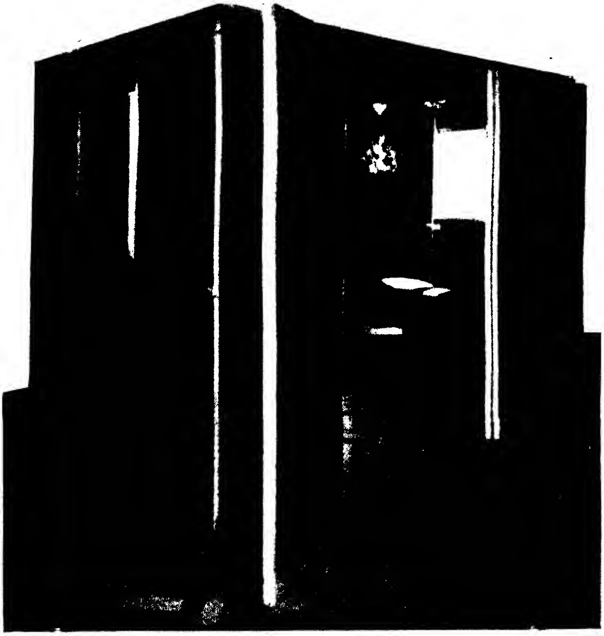


Fig. 1.—Portable air-conditioned cubicle. (*Courtesy, Newcon Industries, Ltd.*)

Acting on these principles, Crowden and Angus have devised a form of portable air-conditioned cubicle. It consists of twenty-one panels, which clip together to make a small room, 10 ft. × 6 ft. × 7 ft. high. The walls are insulated by reinforced aluminium foil in the air space, which prevents the penetration of heat from outside and lessens the load on the small air-conditioning unit serving the cubicle. A power consumption of less than 800 watts has been found adequate for air-conditioning the cubicle under extreme conditions of tropical heat and humidity. It is possible to maintain a temperature of 80.5° F. dry-bulb, 71° F. wet-bulb, 67° F. dew-point, and 65 per cent. relative humidity, with an outside climate of 95° F. dry-bulb, 90° F. wet-bulb, and 88° F. dew-point temperature, with a relative humidity of 82 per cent. The use of such cubicles in tropical bungalows, offices,

factories, hospital wards, ambulance rooms and in mines should go far to eliminate the trials of a tropical climate and maintain normal health (Fig. 1).

NUTRITION IN THE TROPICS

The problem of nutrition is of fundamental importance, and the practical application of its main principles to tropical native races has only comparatively recently attracted the attention which it deserves. Even yet, however, as regards its wider implications, the problem is little understood. The whole subject is another illustration of the parable of the soil and the seed. Defective nutrition arising from unbalanced and unsuitable dietaries is now known to be responsible for many of the ills of mankind, and to predispose, indirectly, to parasitic infection. Within the space available it is only possible to deal with an outline of the principles involved.

The constituents of food may be classified as proteins, fats, carbohydrates, minerals, vitamins and water. The functions of these substances are so interconnected that those of any one group must be considered in reference to the others, for, although proteins are necessary for the building up of the body, they can also be drawn upon for the production of heat and work. Again, although the greater amount of carbohydrates and fats are used for this purpose, yet some are also used for building up the proteins of the cells of the body. The vitamins are usually known as accessory food factors, and are concerned in metabolic processes (*see* p. 425).

Carbohydrates.—The carbohydrates include sugars and starches they constitute the cheapest source of energy and make up the great bulk of the food of man in most parts of the world. They are divided into monosaccharides and polysaccharides. *Monosaccharides* are easily soluble, and diffuse through the alimentary tract, without being acted upon by the digestive enzymes.

The three commonest monosaccharides are glucose, fructose and galactose, and when consumed in larger quantities than are required for the immediate purposes of the body they are built up into the polysaccharide *glycogen*, which is stored in the liver and reconverted into glucose when required for the maintenance of the normal amount in the blood.

Glucose (dextrose, grape sugar) is abundant in many fruits and vegetables and is also the product of the action of digestive enzymes on all starches.

Galactose is formed, together with glucose, when the digestive enzymes act upon the disaccharide lactose (milk sugar).

Disaccharides are converted into monosaccharides during digestion. Three of them, viz., saccharose, lactose and maltose are important constituents of food. *Saccharose* is *cane* or *beet* sugar. Pineapples and carrots are particularly rich in it. *Lactose* constitutes 4–5 per cent. of cows' milk and 6–7 per cent. of human milk. *Maltose* occurs in germinating cereals, malt and malt products.

Polysaccharides.—Most of these are insoluble in water. Those available for food are broken up by digestive enzymes into glucose. *Starch* is stored up in plants, especially in seeds and tubers, for requirements of energy and growth. The action of digestion is to break up the molecules of starch and

convert them into soluble *dextrin*. *Glycogen* occurs in all parts of the body, especially in the liver; there are considerable quantities in the muscles and it is rapidly used up during active muscular exercise. *Cellulose* is resistant to the action of digestive enzymes, and gives bulk to the food and appears unchanged in the fæces.

Fats.—*Fats and lipoids* are substances which are soluble in ether, chloroform, or benzene, but insoluble in water. Examples of edible oils are olive and coconut oil.

The fats are compounds of glycerol and fatty acids. When fat is treated with a strong alkali, the glycerol is freed, and the alkali combines with the fatty acid to form a soap.

Fatty acids lend consistency to fats. The better known are butyric, caprylic, capric, lauric, myristic, palmitic and stearic acids. The last three are solid under ordinary temperature conditions of the tropics.

The other series of fatty acids have general formulæ in which the number of hydrogen atoms is less than double the number of carbon atoms. They are called *unsaturated fatty acids* and can take up iodine (or other halogens). Soft fats, or oils, which are rich in unsaturated fatty acids can be hardened to a desired consistency by hydrogenation.

The fats are composed of the same three elements as carbohydrates but are superior to them as a supply of energy and for storage. Fats can be synthesized from carbohydrates in the animal body.

Lipoids are not allied to fats in chemical constitution. They are present in the tissues of animals and plants, and are necessary for many vital functions; but the relationship of those taken with the food to those in the body cells is unknown. The *sterols* occur widely in living matter, and when ergosterol is irradiated with ultraviolet light, *calciferol* is produced, which has the physiological properties of vitamin D (*see* p. 432).

Proteins.—The proteins are the chief constituents of all the cells of the body, and form the greater part of all the organs and muscles. All contain the five elements, carbon, nitrogen, hydrogen, oxygen and sulphur.

On hydrolysis, or by the processes of digestion, substances of progressively smaller molecular weights are produced—proteoses first, then peptones, and finally amino-acids, of which twenty-one are known. The amino-acids constitute the nuclei around which the proteins are built, and the different permutations allow an almost infinite number of proteins to be constituted.

The amino-acids are all compounds of the NH_2 group, with various organic acids. Examples are: glycin, alanin, leucin, aspartic acid, arginine, histidine, and tryptophane. Some proteins are rich in amino-acids, and poor in others, and there are some proteins such as *zein* of maize and gelatin which do not contain any of the important amino-acids. There is a great deal of evidence to show that the nutritive value of proteins is dependent upon the kind and proportion of these acids. Thus, if young rats are fed on zein, which contains no tryptophane, they fail to grow, but recover when this substance is added.

Amino-acids essential in the food are lysine, tryptophane, histidine, cystin, methionine, phenylalanin, leucin, isoleucin, valin and theonine.

Cystin and methionine both contain sulphur and are particularly required for the growth and maintenance of the skin, which is rich in sulphur. There are some, such as prolin and arginine which, capable of synthesis in the body, may not be necessary in the diet of adults, yet cannot be formed fast enough for the needs of normal growth, and hence are necessary for the diet of children.

Proteins have been classified into three groups as regards their nutritive value :—

(1) "Complete," when one of these is the only protein in the diet, and in sufficient quantity, it can maintain life and support normal growth. Casein and lactalbumin, ovalbumin, glycinin of the soya bean, and gluletin of maize, are examples of these.

(2) "Partially incomplete" : These can maintain life, but cannot support normal growth. Gliadin of wheat, and hordein of barley and prolamin of rye are examples.

(3) "Incomplete" : These are incapable of maintaining life, or supporting growth. Zein of maize and gelatin are examples.

The body requires a steady supply of protein for the repair of the tissues, such as the hormones. The muscles, when at work, utilize carbohydrates and are not breaking down their proteins to more than a very small extent.

It has been determined that about 3 grm. of nitrogen represents the endogenous expenditure of a man weighing about 154 lb., corresponding to about 18.75 grm. of protein for the maintenance of the body, but this is apparently far too low for a routine dietary allowance.

The term *digestive utilization* is employed for the fact that the proteins of various foodstuffs are not equally digested or absorbed. The digestive utilization of meat, fish and milk is definitely higher than that of products of vegetable origin.

Biological value is a term used to express numerically the ability of proteins to satisfy the nitrogenous needs of the body. The numerical figures give some indication of their comparative values. Thus, of animal products, beef muscle is reckoned at 98, and shell-fish at 72, whilst maize flour is standardized at 60. The quality of a protein for body maintenance of the adult can be expressed in numerical terms, but this is not the case with children and adolescents, because their relative requirements are continually changing : thus a protein of poor value in the early stages of life may become more valuable in later years when growth requirements are declining and needs of maintenance increasing.

As regards the period of growth it is shown that the proteins of animal origin have a marked superiority over those of vegetable origin, and amongst the former milk holds pride of place for growth-promoting properties.

The protein requirements of pregnancy can be easily estimated. The fœtus and adnexa contain an average of 100 grm. of nitrogen, which may be represented as 625 grm. of protein. This amount is built up in 270 days of pregnancy, and thus the mean production is 2·3 grm. When this is added to the maintenance requirements the total is 17·5 + 2·3 = 19·8 grm., but the protein needs are not evenly spread over the whole period of pregnancy, less being required during the earlier than during the later months. A woman during pregnancy, however, is able to store proteins as a reserve against the demands made upon her during lactation.

There are some common *diseases* of the tropics which greatly increase the metabolic rate, and, although carbohydrates and fats are mainly affected, the increased output of nitrogen and the wasting of muscles indicate an increase in the breaking down of the proteins. Malaria is one of these, and so are the prolonged fevers of the typhus, typhoid and undulant groups. An adequate diet should contain proteins from a variety of foodstuffs, so that all the necessary amino-acids will be present in adequate amounts.

Products of animal origin supplement cereals better than vegetable products for the needs of growth.

Minerals.—Many minerals are present in the body; for instance, calcium, phosphorus, potassium, sulphur, sodium, chlorine, magnesium, iron, manganese and iodine, with traces of copper, zinc, fluorine, silicon and aluminium. All these elements in the human body are necessary for growth and health, as they enter into the constitution of all the tissues, and in the case of the bones and teeth they are present in large amounts as soluble salts in all the fluids of the body, where they maintain neutrality, osmotic pressure and solvent powers, supply electrolytes for the action of muscles and nerves, and produce acidity or alkalinity in the digestive and other secretions.

A healthy, active man excretes daily from 20–30 grm. of mineral salts in the form of chlorides, sulphates and phosphates of sodium, potassium and calcium, and small amounts of ammonium salts derived from protein metabolism.

The taking of salt with food supplies the necessary amount of sodium chloride. The quantity of different minerals in foodstuffs of vegetable origin is directly dependent on the nature of the soil on which they are cultivated.

Some minerals are present in all possible human diets in quantities considerably greater than the needs of the body. Sodium chloride, for instance, is present in quantities in most human diets, but there are tribes in Central Africa to whom common salt is not easily accessible, so that the custom of using mineral earth or plant ash has developed.

Manganese has been shown to be essential for growth and health, and is present in vegetable in far greater quantity than in animal tissue.

Sulphur.—By far the greater proportion of this element in the tissues is derived from the proteins of the food.

Calcium, phosphorus, iron and *iodine* have been shown in various parts of the world to be deficient in human diets.

The greater proportion of the calcium and phosphorus in the body is present in the bones and teeth. Calcium and phosphorus are liberally supplied in the milk of all species of animals. Diets deficient in calcium are referable to the skeletal structures. The term *pica* is applied to certain manifestations of a depraved appetite, such as earth-eating or bone-chewing, frequently seen in native people. It should be accepted as a sign of mineral deficiency. When stunted growth and decay of teeth are prevalent the adequacy of the amounts of calcium and phosphorus in the diets has to be considered.

Iron is present in the body in small amounts, and its functions are of vital importance since it is an essential element in the formation of the hæmoglobin of the blood, which contains thirty times more iron than does the rest of the body.

When blood-corpuscles become effete and are broken up, the greater part of the iron is not lost, but is retained in the body and used again for the formation of hæmoglobin.

Microcytic hypochromic anæmia, which is very common in the tropics, especially in ancylostomiasis, is due to an iron deficiency. During pregnancy there is a withdrawal of iron from the mother's body to supply the fœtus.

Iodine is necessary for the formation of thyroxin, the hormone of the thyroid gland which regulates the metabolism of the body. There are

about 15 mgm. of iodine in the thyroid gland of an adult man, but only 10 mgm. in the rest of his body.

Iodine is present in sea-water, and the products of the sea, such as fish, seaweed and salt contain appreciable quantities of it.

The Energy Value of Food

The energy value of food is supplied by the carbohydrates, fats and proteins, and is expressed in terms of heat-units or *calories*. The definition of a *calorie* is the amount of heat required to raise the temperature of one kilogramme of distilled water one degree Centigrade.

The apparatus utilized for the purpose of determining calorie values is *Atwater's bomb calorimeter*. The heat of combustion of organic substances depends upon their chemical composition. The total energy requirements of the body are conveniently expressed in calories per day, either for the whole body, or per kilogramme of body weight, and the quantities of food in terms of calories which are necessary to support normal metabolic processes may be studied from the point of view of requirements for *basal metabolism*, requirements for *general maintenance*, and requirements for *work*. The recommendations of the League of Nations in reference to energy requirements are as follows :

For an adult man or woman living in a temperate climate, an allowance of 2,400 calories is considered adequate, but the following supplements for muscular activity are to be added. For light work 75 calories per hour of work, and for very hard work 300 calories per hour of work.

It has been determined that the average size of most tropical races depends largely on the status in life, but taking the populations as a whole, the mean sizes are smaller than for populations living in temperate climates.

The mean weights of men and women of most tropical races is about 115 lb. for the former and 100 lb. for the latter. It therefore follows that the maintenance allowance of 2,400 calories is too high, and 2,100 calories is sufficient, whilst the energy value of the food of the average labourer in the tropics may be placed at 2,600–2,700 calories *per diem*.

The balancing of diets for poorer classes of natives, so that the proteins shall be adequate in quality and quantity, obviously presents many difficulties. It is generally accepted that the daily protein allowance should be 100 grm., with the proviso that it shall include 37 grm. of protein of animal origin ; but the figures accepted for temperate regions are too high for the tropics, and the figures given for India are considerably lower. There the requirements for men are 65 grm. ; for women 55 ; for growing boys 80, and adolescent girls 70 grm. *per diem*.

The weight of fat in the diet should be about the same as that of proteins, and should not fall below 50 grm. daily. Butter and ghee are preferable to vegetable oils. The main function of the carbo-

hydrates is to supply calories in all cases where additional energy is required for work. This should be supplied by foodstuffs rich in carbohydrates, such as rice, bread and other cereal foods.

The calories of a diet consisting mainly of rice, dhal, coconut and green vegetables, such as is commonly in use throughout India and Southern Asia, are sufficient for the average man and the proteins, although not of a high biological value, are just enough for an adult, but such a dietary is usually deficient in calcium, while the supply of adequate protein of high biological value is not sufficient for the needs of growth and maternity, but the addition of fish increases the supply of calcium as well as of protein.

The effect of dietary upon the physique and health of tropical natives has been made the subject of a special study by Orr and Gilks (1931). A survey of two tribes in East Africa, the Masai and the Kikuyu, were made. The former subsist mainly on milk, meat and raw blood, and on an average are 5 in. taller, 23 lb. heavier and 50 per cent. stronger than the latter, who live mainly on cereals, roots and fruit. Marked differences were found in the incidence of disease in the two tribes. Bony deformities, dental caries, anæmia, pulmonary conditions and tropical ulcer are very much more prevalent in the Kikuyu, whilst intestinal stasis and rheumatoid arthritis are more common amongst the Masai.

Tables of the nutritional value of the main foodstuffs of Central African natives have been prepared by the Imperial Bureau of Animal Nutrition—as it is generally agreed that the native must have better food if he has to have better health. It is admitted that it is difficult to assess the effects of different diets upon particular native peoples, since little is understood regarding the metabolism of African natives.

There is no doubt that improved nutrition calculated upon a scientific basis should confer enormous benefits upon the British Colonial Empire, and indeed upon all natives of the tropics, not only in the eradication of deficiency diseases, but also in reducing the very high infantile mortality which is to be found almost everywhere. The question has formed the subject of a searching enquiry by a Government Committee on Nutrition in the Colonial Empire (February, 1939).

One of the most striking outcomes of this enquiry has been to show the almost complete absence from tropical diets of milk, or indeed of animal products, in all native communities, with the possible exception of the West Indies. Another striking fact which has emerged from this survey is the extent to which native peoples are dependent on a *single crop* for their main supply of food. Indeed, it may be said, as compared with the European a low standard of living is almost universal. With such a diverse range of climates, environment, peoples, customs, prejudices and beliefs, it becomes almost impossible to generalize, so that the kind of diet which will give the best results must always be worked out on the spot for each territory. Ignorance,

tradition and prejudice remain the most important factors in this problem.

In working out the energy requirements of the body in native communities, recent work has shown that the formula should be computed upon the surface area of the body. The formula commonly employed is that of Du Bois, which is as follows:

Surface area in sq. centimetres = wt. in kilos. $\times 0{\cdot}425$ + height $\times$ $0{\cdot}725$ + $71{\cdot}84$ (a constant).

It has already been stated that the biological value of food for the human subject may vary very considerably, and as regards the variation in chemical composition, it is common knowledge that the soil in which a foodstuff is grown, the method of manuring, the time and method of harvesting, the methods of storing, marketing, processing and cooking, all have a very marked effect upon the value of the food as consumed, so that a proper allowance has to be made for all these factors. As regards the power of the individual to benefit from the food he eats, there are many factors which react upon the state of nutrition by affecting the metabolic processes in the body, such as the hygienic surroundings, high humidity, traumatic states and pathological processes which interfere with the powers of absorption. Against this also is the possible action of *toxic substances* in the food. In the examination of native dietaries, it should be remembered that untoward results may be due to cyanides, fluorides, and even the result of parasitic growths and contamination from storage.

The more obvious feature of native diets is that, with a few exceptions, they are predominantly vegetarian in nature and that relatively small quantities of animal products are consumed. Maize, rice, millets, guinea-corn, groundnuts, beans, peas, cassava, yams, coco-yams, tannias, sweet potatoes, plantains, bananas, gourds, coconuts and other palm products and numerous leafy vegetables are the main raw material of vegetable origin from which dietaries are composed.

It is therefore apparent that the outstanding feature of their diet is that, judged by European standards, an unusually high proportion of the energy value of the diet is derived from carbohydrates. This is therefore at the expense of the amount of fat in the diet which is usually very low, except in areas where coconuts (as in Malaya and the Pacific) or other palm products (in South Nigeria and West Africa) are largely consumed. *Since it is necessary* to consume two and a quarter times as much carbohydrate, by weight, to obtain the same amount of energy as from one unit of fat, it follows that the diets are also bulky relative to their nutritive value.

This does not by any means imply that most native races eat *too much food*—much more often they eat a great deal less than they ought to do. Although, under the present circumstances, there is no actual famine, yet there is frequently a shortage owing to bad harvests, plague, locusts and economic stringencies. If the diets are unduly bulky, the bulk is made up of foodstuffs unsuitable for nutrition.

The diet of pastoral tribes of Kenya and Tanganyika consists chiefly of meat, blood and milk, and in North Nigeria also animal products are easily obtainable, whilst to the nomad Somali, camel's milk is the staple article of food, but these are quite exceptional cases. Wherever meat is available it is poor in quality, deficient in fat, and far too expensive for the poorer classes. Fish is most used by those to whom it is easily available on the seaboards, river or lakeside, and is commonly eaten fresh or dried, but with the exception of the Pacific Islanders it does not constitute the main article of diet. There is a general deficiency of fats and, when procurable, they are drawn from vegetable sources. This is deleterious as fats act as vehicles for vitamins A and D. Added to this, there is a deficiency in the consumption of leafy vegetables and fruits, and therefore of vitamin C.

Beriberi (p. 435), which is recognized as a deficiency of vitamin B_1, occurs most frequently in countries where rice is the staple article of food, in China and Malaya. In the Straits Settlements it still causes, on an average, 900 deaths a year.

It is probably correct to state that, beyond the well-established diseases, there are a great many borderline cases, where comparative malnutrition leads to a general lowering of the standard of health without eliciting the recognized symptoms of the classical disease.

Special crops which should be encouraged from the point of view of nutrition are now receiving special attention, and amongst these the soya bean (*Glycine hispida*) and the groundnut (*Arachis hypogæa*) are worthy of special mention, for they both contain protein of good biological value and a high proportion of fat. The groundnut contains between 20 and 30 per cent. of good protein and as much as 40 to 50 per cent. of fat. The soya bean is particularly rich in calcium, and the groundnut in vitamin B_1, and in general, as regards its mineral, fat and protein content, compares favourably with most vegetables. Unfortunately, it is not an easy crop to establish. There are other legumes which are of special value as foodstuffs—such are the pigeon pea (*Cajanus cajan*), cow peas (*Vigna unguiculata*), black and green grams (*Phaseolus mungo and P. aureus*), tepary bean (*P. acutifolius*), Lima bean (*P. lunatus*), dolichos bean (*Dolichos lablab*), and haricot bean (*P. vulgaris*).

There are a number of other vegetables which are of nutritive value, including the yams and potatoes. The red and yellow sweet potatoes are good sources of the precursors of vitamins A and C. As regards oils and fats, of which there is generally a deficiency, there are found several oil palms in West Africa, especially the red palm oil obtained from the fleshy pericarp of the fruit of the oil palm, *Elæis guinensis*, which, as far as vitamin A is concerned, is equal to good cod-liver oil. The kernels also contain a special oil known as "palm kernel oil," which is also used in food and for a great many other purposes. The cultivation of these oil palms is a special industry in West Africa and they have now been exported to Sumatra and the West

Indies. The importation of this palm is to be encouraged wherever the soil and climate are suitable. "Shea butter" is obtained from the nuts of the wild shea tree (*Butyrospermum parkii*) and is also a considerable source of fat.

The principal articles of diet consumed by native races may be stated as follows:

Africa (East Africa, Somaliland, Uganda, Tanganyika, Kenya, Nyasaland):—The natural food of the nomad Somali is milk and meat with additions of ghee, rice, dates. The diet lacks variety, and the imbalance is due to fat excess, resulting from milk and ghee. There is a striking absence of deficiency diseases. In Kenya different tribes have entirely different dietetic habits. The diet of the Masai consists chiefly of meat, blood and milk, whilst that of the Kikuyu and indeed most others, is composed of maize, tubers and legumes. In Tanganyika the diet consists of millet, mtama, maize, rice, groundnuts, beans, cassava (*Manihot utilissima*), sweet potatoes (*Ipomœa batatas*), and occasionally fish and meat, mutton, goat's flesh, milk and blood. Tabus and tradition are important factors in dietary shortages, and a tabu on eggs and milk may operate even during a time of shortage. Owing to trypanosomiasis, the people in two-thirds of the territory are prevented from keeping domestic animals. In Uganda the diet is chiefly vegetarian. Plantains form the staple article in parts of the eastern, northern and western provinces; in the rest of the country grain is the staple, the small millet (eleusine) being the commonest. Again beans and peas may be the staple. Sweet potatoes, great millet (sorghum), cassava, simsim, pumpkins, gourds and native spinach are secondary foods. Locusts, grasshoppers and white ants are universally eaten as delicacies.

In Nyasaland maize is the staple foodstuff, except in areas where the soil is unsuitable and cassava is relied upon. The staple food, whether maize cassava or millet, is eaten in the form of a porridge. The amount of milk consumed varies from tribe to tribe, but is not taken by adults. Eggs are neglected by tribal tabus. The intake of first-class protein is entirely inadequate. Throughout West Africa the nutritional level is considerably higher than in the Central portion or on the East Coast, and there is a great variety of proteins and fats.

In the Northern portion, on the Gambia, where seasonal crops are grown, the staple article of diet is imported rice, but in the winter months, millet and guinea corn take its place. Secondary foods are yams, coco-yams, cassava, pigeon pea, ragi, okro, pumpkin, tomatoes, citrus and other fruits. On the Gold Coast, and Sierra Leone, the staple articles of diet in the northern territories are millet, guinea corn, yams, Fra-Fra potatoes, supplemented by maize, groundnuts, tomatoes, onions and shea butter. This latter, which is a most important supply of oil and fat, is obtained from the nuts of the wild shea tree, which grows in a wild state, especially in Northern Nigeria and the Gold Coast; it has recently been introduced into Uganda and other parts of East Africa. In the southern portions there are in addition plantains, meat and fish. In Nigeria, beans, milk, eggs, meat and green vegetables are procurable, and also a certain amount of honey, and there is an abundant supply of shea butter.

In *Malaya, the East Indies and Southern China* the available food supply is

wide and varied, and is ample in most towns if the resources are at hand to purchase it. Rice is the most important food, and is supplemented with vegetables of the root variety, leaves and pulses. Fat supplies in Malaya are obtained from the red unbleached palm oil produced locally, which is a source of vitamin A. On the whole there is deficiency of vitamin B products and protein.

India and Ceylon present a special problem on account of their highly industrialized state and on account of the diversity of the population. The Hindoos, for instance, are precluded by their religion from eating meat. The staple articles are rice, most of which is polished, coconut, leafy vegetables, yams, tubers, beans, lentils, peas, dhals and gourds, which are cooked into curries of various types. Curry stuffs consist of chillies, coriander, saffron, garlic, nutmegs and fish ; the latter is the principal foodstuff of animal origin eaten by the poorer classes. Milk seldom enters into the dietary. The diet in the towns is superior to that in the rural areas. Tea is the principal beverage in Ceylon and in South India, and toddy made from fermented sap of coconut is also widely used, and the toddy yeast is rich in vitamin B. The most serious deficiencies in the diets of the masses are of animal protein, calcium, and vitamins A and B complexes. To improve the calcium content a greater use of small fish and leafy vegetables is advocated.

Nicholls in Ceylon has shown the food value of the egg-plant (*Solanum melogena*), and has analysed the substances in the edible portion, as reported from five countries. The highest protein content is from Malaya (2·2 per cent.), whilst the lowest is in Java (1·0 per cent.), and the calcium and iron contents also vary proportionately. Orr has stated that in no part of the world is the problem of nutrition to be more seriously studied than in India, where there are only two rice bowls for three mouths. The fundamental difficulty is shortage of food, and the problem is one of agricultural reorientation and development to provide more food, and especially milk and other protective foods for human consumption.

West Indies and South America.—The average diet of the working classes in Barbados, Jamaica and other West Indian islands consists chiefly of rice, flour and other cereals, sweet potatoes, yams, onions, salt pork or beef, salt fish, sugar and tea. Milk consumption is low, and in the majority of cases the condensed preparation is used. There is a shortage of milk, eggs and fresh vegetables. The weekly wage of parents does not usually suffice to feed the whole family for a week, so that the children, after the middle of the week, receive no regular meals. In Jamaica cows' milk is rarely taken, even when available. Fat, of which the chief source is coconut oil, is deficient in the majority of diets. Vegetables, such as pumpkins, onions and tomatoes are not extensively used. Special stress is laid upon the shortage of protein in the island products. A high percentage of the population suffer from varying degrees of subnormal nutrition.

In *British Guiana, Venezuela, Brazil* and the tropical portions of South America, rice is grown over wide areas and is the staple article of food for more than a quarter of the population, and maize is grown to some extent. Sweet potatoes, tannias, yams, cassava, bananas, plantains and bread fruit are commonly used. Although there is usually a protein deficiency, there cannot be said to be a shortage of fresh meat, and there are many varieties of local fish, whilst eggs and milk are fairly plentiful. The main difficulty about the milk is its unsatisfactory quality, due to adulteration and contamination. Fats are generally deficient and are obtainable mostly from coconuts and avocado pears.

Rice (*see* p. 438)

Rice forms the staple food of nearly one-half of the world's population. It is at present being produced in amounts sufficient to supply one-fifth of the caloric requirements *per capita* per annum. It is estimated that there are about 200 million acres of land under rice cultivation, and two-thirds of the area are shared equally between China and British India, and about 60 per cent. of the world production is grown in the British Empire. The peoples who subsist on rice consume as much as 80–90 per cent. of it as the total food intake.

The proteins of rice are of a good quality, their biological value for man approximates very closely to that of beef, and the amino-acids compare in amounts very favourably with that contained in other proteins, but the mineral constituents are low and the needs for calcium and phosphorus are not met by either unmilled or polished rice (*see* p. 438).

It is realized that, during storage, serious changes detrimental to the food value of rice may occur, and this in native hands unfortunately frequently takes place. It is possible to feed on rice which has been well milled, as a sole and staple food, without developing any signs of beriberi, provided that the rice is stored under conditions so that its vitamin B_1 is not lost.

It has been established that rice can be stored without its husk with as good or better results than those obtained with rice stored with its husk on. Rice should not be over-washed before cooking. The widely used method of processing is known as "parboiling," and consists of soaking rough rice in either cold or hot water in cement or metal tanks. After draining off the water, the rice grains are submitted to steam till the hulls are opened slightly. This soaking process may last four days. On a diet of parboiled rice no less than 150 international units of vitamin B_1 must be supplied daily in other components of the diet (as, for instance, by 6 oz. of dried beans or 3 oz. of groundnuts).

The cooking of rice must be carried out in a manner in which there is retention of vitamin B_1.

When conditions are obtained for optimal production, it is found that there is no food crop of comparable nutritional value which can approach rice in the amount of food produced in a given area, and in its suitability as a food for man in the character and proportion of its ingredients.

THE TROPICAL ANÆMIAS

There are so many varied parasitic infections in the tropics that *anæmia,* as a clinical feature, is almost universally observed. Besides that due to the very active hæmolysin-producing parasites, of which malaria and the ancylostome are the most important, every kind of anæmia which is familiar from a study of general medicine is somewhere to be found. In the appropriate place in the text of the present work the particular kind of anæmia associated with a particular species of infection will be mentioned, but in addition to these there are *idiopathic anæmias* peculiar to the tropics having features peculiar to themselves. It has therefore been considered advisable to introduce a special section on this subject, especially as the scientific study of the anæmias has been placed upon a new basis as the result of modern intensive research.

Macrocytic Anæmia of Pregnancy

Synonym.—Tropical macrocytic anæmia.

Macrocytic anæmia has for some time past been recognized in India, Malaya, West Africa and other parts of the tropics, in pregnant women. In the former country it has been differentiated by Wills and others from the " pernicious anæmia " of pregnancy which occurs in temperate climates. The macrocytic anæmia of pregnancy is gradual in its onset during the second month, but the final breakdown may be sudden. As in pernicious anæmia, many of the clinical features are referable to the decrease in the number of red blood-corpuscles. The tongue may be sore, but nerve changes are absent, and the oxyntic cells of the stomach secrete hydrochloric acid. Œdema of the feet and ankles is associated with low blood-pressure and pyrexia. Retinal hæmorrhages are common. This macrocytic anæmia of pregnancy is essentially due to dietetic deficiencies, aggravated by superadded infections of malaria and ancylostomiasis, and there appears, therefore, to be no essential difference between the macrocytic anæmia of pregnancy, as described by Wills and Mehta in India, and the nutritional macrocytic anæmia which has been made the subject of special studies in Macedonia by Fairley, Bromfield and Kondi. In the case of macrocytic anæmia of pregnancy, many patients survive to term but collapse during parturition. Premature labour is usual, unless the disease is treated in time. Cases with anæmia, when associated with albuminuria, sometimes suggest toxæmia of pregnancy. If this condition is recognized in time and treated by blood transfusions and liver therapy, patients may proceed to term, but the children, though not themselves anæmic, are feeble. The response of this type of anæmia to liver therapy suggests that it is due to the lack of hæmopoietic principle.

For a clearer understanding of this subject it is necessary to describe the processes by which these blood changes are produced :

(1) *Reticulo-endothelial stage*
Development into megaloblasts. Interference at this stage produces *aplastic* or *normocytic anœmia.*

(2) *Megaloblastic stage*
Development into normoblasts. Interference at this stage produces *megalocytic anœmia.*

(3) *Normoblastic stage*
Development into erythrocytes. Interference at this stage produces *microcytic anœmia.*

Megalocytosis.—*Megaloblasts,* when hindered during their normal development, produce a certain number of megalocytes, which then enter the circulation and cause an increase in the average size (megalocytosis), with consequent reduction in the total number. The total amount of hæmoglobin falls in conjunction with the above.

The colour index rises owing to the increased proportion of

hæmoglobin (saturated megalocytes). At the same time, megaloblasts are almost invariably present.

Summary of present knowledge of essential factors.—It is thought that the normal individual obtains the factors necessary for blood regeneration from the interaction of an *intrinsic* factor in the gastric juice, and an *extrinsic* factor which exists in food. The result of the interactions of these two factors is absorbed from the intestines and stored in the liver and other abdominal organs. Addisonian or pernicious anæmia certainly arises from a deficiency of the *gastric* factor ; but the syndrome of macrocytic anæmia may arise principally from a dietary deficiency. Thus in sprue, idiopathic steatorrhœa and intestinal stenosis, hydrochloric acid is present in the gastric juice, and the presence of Castle's intrinsic factor has been demonstrated, yet the macrocytic type of anæmia is identical with that found in pregnancy and in nutritional megalocytic anæmia. In pregnancy a latent partial deficiency may become manifest owing to the demands of the fœtus for hæmopoietic material. Some alteration in the internal metabolism of " liver extract " is thought to occur in certain cases, and to account for the macrocytic anæmia, frequently found in liver cirrhosis, and in tropical nutritional anæmia, and which is affected by superadded infections, such as malaria. The anæmias of deficient nutrition, like the avitaminoses, are the result of variable participation of a number of circumstances affecting the intake, absorption and utilization of essential food factors.

The hæmopoietic substance, or P.A. factor.—The mode of formation has been elucidated by the discovery of various substances in the cure of pernicious anæmia. Active substances given by mouth, in order of preference, are—liver, liver extract, hog's stomach, gastric juice digested with beef, gastric juice with yeast (vitamin B_1 and B_2). The active preparation on injection is liver extract. The production of hæmopoietic substance is produced by the interaction of :

Intrinsic factor, secreted from the pyloric end of stomach and duodenum, probably by Brunner's glands. This secretion may be prevented by some unknown lesion.

Extrinsic factor, the nature of which is unknown. Closely associated with the vitamin B complex, it is present in most mixed diets.

Megalocytic anæmia therefore develops if hæmopoietic substance is defective and its action on bone-marrow inefficient. Deficiency may result from intrinsic factors. Extrinsic factors arise as the result of absorption from intestine—and errors of storage. Several of these factors may operate simultaneously.

Nutritional Macrocytic Anæmia

As this form occurs among tropical peoples, it is probably universal wherever the population is living on an unbalanced and deficient protein dietary. Nutritional anæmia is associated frequently with

malaria and syphilis, and in India also with ancylostomiasis. Fairley, Bromfield and Kondi now recognize a *macrocytic hæmolytic type*, which is prevalent in Macedonia, and is accompanied by splenomegaly due to chronic malaria infection. In this type there is a primary nutritional deficiency with a hæmolytic agent—the malaria parasite—superadded. Males as well as females are affected. In addition to the anæmia there is a tendency to leucopenia with a shift to the left and a decrease in the platelet-count.

The anæmia is distinctly macrocytic. The average corpuscular diameter is about 8·6 μ. The red cells are, as in pernicious anæmia,

Fig. 2.—Sickle cells. Fresh blood preparation after forty-eight hours. (*Bulletin of the Johns Hopkins Hospital.*)

more reduced than the hæmoglobin. There is much anisocytosis, but less poikilocytosis than in pernicious anæmia.

Treatment.—This anæmia responds to liver or liver extracts quickly —it is said that anahæmin is not effective.

Differential diagnosis.—In pernicious anæmia there is achlorhydria and a positive van den Bergh reaction, whilst in tropical nutritional anæmia the opposite is the case. Glossitis is said to be much more common than in pernicious anæmia. Tropical nutritional anæmia has also to be distinguished from the macrocytic anæmia of sprue.

Sickle-cell Anæmia

Sickle-cell anæmia is a severe hæmolytic anæmia in which the red cells assume a peculiar sickle shape (Fig. 2). It occurs almost exclusively

among negroes. The disease is characterized by remissions and exacerbations of the anæmia, associated with joint pains and a tendency to ulceration of the legs. First described by Herrick in 1910, it has formed the basis of a fine study by Huck (1923). This disease is the most common primary blood dyscrasia of negroes, and nearly all the cases have been described in members of that race in the United States. On the whole, it is a rare disease, and the sickle cell trait is present in 5–7 per cent. of all American negroes, quite irrespective of whether they are healthy or not. Sometimes it is found in mulattos. Rosenfeld and Pincus have found it in Italians, Cooley and Lee in Greeks, Sights and Simon in white Americans, and Wallace and Killingsworth in Mexicans. It has also been found in wild deer in America.

Although this disease must have originated in West Africa, whence it was imported into the United States, comparatively few cases have been recognized in that continent. There are a few records, e.g., by Archibald, of a case in an Arab, from the Sudan (1926), and other scattered records from Nigeria and the Gold Coast (Russell and Taylor, 1932). It is an hereditary and familial disease with a Mendelian dominancy, and is transmitted equally by male or female. It must be remembered that the sickle cell trait is not invariably associated with anæmia. Sickle-cell anæmia has to be distinguished from ovalocytosis, which is a hereditary familial condition, in which the elliptical shape of the red cells (like those of the camel) is transmitted in a Mendelian manner. In this state, it has been shown that the young red cells in the bone-marrow have the normal round shape, and they only assume an oval form when they become mature. Cooley and Lee have drawn attention to the probable tribal origin of sickle-cell anæmia in West Africa.

Sickle-cell anæmia begins in childhood, and males are affected three times as frequently as females. It has been noted that symptoms of the disease may present themselves at seventy-eight years of age. The red cells are larger than normal, and show either a normal or decreased fragility. The sickling develops usually only after the blood has been taken. Ordinary stained blood films do not reveal the sickle shape of the red cells except in very severe cases. The non-recognition of this fact is probably due to the comparatively few instances which have been recorded. The wet-blood films should be ringed with vaseline and allowed to stand overnight. Cooley and Lee have shown (1926) that in preparations kept in the incubator the sickle cells disappear, leaving the normal round cells intact.

The latent phase of the disease is much commoner than the active one; in this the red cells in the circulation do not circulate as such, and only a few actual sickles can be found in perfectly fresh blood. In fresh preparations large endothelial cells may be seen engulfing red corpuscles. Nucleated red cells are always present (Cook and Meyer, 1915). In severe cases the red cells are reduced to 2–3 million, and the leucocytes increased to 15,000 per cu.mm. Basophilic stippling of

the red cells is common and the blood platelets are not diminished (Mason, 1922).

Pathology.—The bone-marrow is hyperplastic and contains sickle cells. The spleen may be enlarged or may be trophic and fibrotic. Osteoporosis of the bones is commonly observed. Rich has described lesions in the spleen which are considered characteristic. There is a congenital malformation of the sinuses, which permits free escape of blood into the pulp, and this is especially marked round the Malpighian bodies. In formalin-fixed specimens alone can the sickle character of the cells be recognized in sections. Graham (1924) has made a minute pathological study of this disease and finds chronic hepatitis and cholelithiasis usually present.

Symptoms.—Sickle-cell anæmia may remain latent throughout life. On the other hand, there may be an active phase causing a severe chronic anæmia of the hæmolytic type, associated with weakness, dyspnœa and a tendency to ulceration of the legs, resembling indurated syphilitic ulcers (Huck), a yellowish discoloration of the scleræ, and jaundice, especially when the blood destruction is very great. The liver and spleen are usually enlarged. There may be thrombi in the small vessels of the lungs, giving rise to symptoms of cardiac disease. There is usually a positive indirect van den Bergh reaction.

When the disease is active there may be intermittent paroxysms of fever, associated with severe joint pains which may last two or three weeks. These patients who exhibit anæmia usually do not live beyond middle age, and death usually takes place from intercurrent infections. The latent disease may be stimulated into activity by any infection.

Blood changes.—Sometimes the blood is macrocytic, and there is a neutrophile leucocytosis of 10,000–30,000. Polychromasia is a marked feature, there is a reticulocytosis of 25 per cent. ; normoblasts are common.

It has been shown that by keeping citrated blood under oil for twenty-four hours, and then adding formalin, the test for sickle-cells becomes very delicate.

Treatment.—The treatment is purely symptomatic. The anæmia may be improved by iron and liver therapy. Blood-transfusion is of distinct value in relieving paroxysms of blood destruction. Splenectomy has been employed with some benefit in selected cases, but the sickling is unaltered by this operation.

Cooley's Anæmia

In 1927 Cooley drew attention to an anæmia—a blood dyscrasia—occurring usually in children of Mediterranean parentage, associated with splenomegaly, a definite mongoloid facies, and characteristic changes in the bones, particularly of the skull and hands. The age of incidence is commonly from six months to three years, but older

children are not exempt. It is closely related to, if not identical with, von Jaksch's "erythroblastæmia of childhood." On account of its predilection for Mediterranean races the condition has somewhat fantastically been described as "thalassæmia." One case has been described by Cooley in an English child, and Moncrieff and Whitby found a typical example in a girl of one year and six months, a child of Greek parents in London.

As a blood dyscrasia appearing in recessive Mediterranean races it is comparable to the sickle-cell anæmia described above. Homologous twins with this condition have been reported. Most cases so far have been reported from America.

Blood changes.—There is a moderately severe anæmia. The red cells number from 2–4 million per cu.mm., with hæmoglobin 4–9 grm. per cent. (30–60 per cent. Haldane), and the colour index is therefore low. The most striking feature is the large number of normoblasts, which may number as many as 200 per hundred leucocytes. True megaloblasts are not found. Anisocytosis is marked with poikilocytosis. There is great variability in the cell size.

There is usually a persistent leucocytosis of 13,000–50,000 cells, and in severe cases a few myeloid cells. There is no increased fragility of the red cells. The indirect van den Bergh reaction is positive.

Clinical features.—The chronic hæmolysis is shown in the skin by pigmentation and by an excess of urobilin in the urine. The pigment distribution in the main resembles that found in hæmochromatosis. There is splenomegaly which is invariable and associated with hypertrophy of the liver and enlargement of lymph-glands.

The patient's features have a peculiar muddy yellow look, associated with a thickening of the cranial bones and malar eminences, giving a peculiar Mongolian appearance. The bony alterations, which are caused by hyperplasia of the bone-marrow, can be demonstrated radiographically and consist of coarse trabeculations and rarefaction. The inner and outer tables of the skull are thinned. Splenectomy has little effect on the course of the disease, which is invariably fatal.

Pathology.—The excised spleen shows a thickened capsule with prominent Malpighian bodies and a mild general fibrosis, and the bone-marrow a marked hæmopoietic reaction. There are islands of megaloblasts. The majority of the myelocytes are eosinophilic.

Ætiology.—Its congenital nature places Cooley's anæmia in the same class as acholuric jaundice, sickle-cell anæmia and, possibly, idiopathic steatorrhœa.

Acholuric jaundice can be excluded by fragility tests, and severe anæmia accompanied by rickets must be considered.

Treatment.—There is no satisfactory treatment. Blood-transfusion is without effect, and liver and iron therapy are useless. The disease is progressive and most patients fail to reach the age of ten.

THE COMMONER DISEASES IN THE TROPICS AND THEIR MODIFICATION BY TROPICAL CONDITIONS

The institution of special schools and courses in tropical medicine and the remarkable discoveries which have been made in this branch of science have tended to foster the idea that tropical diseases necessarily predominate in most tropical countries. This, however, is by no means the case. The fact is that most of the ills which afflict mankind occur nearly everywhere, but their incidence and frequency appear to be influenced by local circumstances. Moreover, the clinical picture of a familiar disease may be modified or masked by some superadded parasitic infection. Indeed, a complex pathology in the tropics is the rule rather than the exception. This subject, which has been named "geographical pathology," has received serious attention during recent years and has provided data of considerable importance. While it is manifestly impossible in a book devoted to tropical diseases to go into the matter in a detailed way, a general survey should not be out of place.

Diseases of the Digestive System

Little is known about the variations in gastric secretion in the tropics, save that in ancylostomiasis and other worm infections the secretion of hydrochloric acid by the oxyntic cells is reduced: but it is a striking fact that *gastric and duodenal* ulcers are seldom encountered in native races living on a simple carbohydrate dietary. This applies especially to Indians, Javanese and Negroes. As the result of 2,170 autopsies, Kouwenaar in Java concluded that ulcers of the stomach and duodenum are found only in 1 per cent. of Javanese as against 10 per cent. of Chinese. Gastric and duodenal ulcers are said to be very common in Abyssinians, and this fact is ascribed to dietetic causes (Bergsma). Wanless finds these ulcers common in rural districts of western India, due to septic mouths and excessive stimulation by hot curries. Diverticulosis and diverticulitis appear to be very rare or almost unknown.

Appendicitis

Inflammation of the appendix is a rare event in native races, and the fulminating cases requiring immediate operation seldom occur, in marked contrast to the frequency of this condition in the European residents. In Indians, both among Moslems and Hindus, acute appendicitis is extremely rare. The Editor has seen only two cases in an experience of over thirty years.

Carcinoma of the Stomach and Intestinal Tract

The rarity of malignant growths in the alimentary tract in native races has been the subject of much speculation. De Langen has laid

special stress on the fact that gastric carcinoma is noticeably absent among the Javanese. The same is true in India and, as far as can be ascertained, in Central Africa. It may be that the comparatively short life-span of the native, in contrast to that of the European, may account for this difference.

Primary Liver-Cell Carcinoma

This condition, which is extremely rare in Europeans, appears nevertheless to be common, especially in the East Indies and West and East Africa, whilst secondary carcinomatous deposits which are such a frequent sequel of abdominal neoplasms in temperate countries are, probably for the reasons already stated, rarely met with. The rarity of carcinoma of the large intestine and rectum has frequently been remarked upon.

Cirrhosis of the Liver

All writers in tropical pathology have laid stress on the frequency of liver cirrhosis with ascites among native races, where the influence of alcohol can be discounted. Some of these cases are due, as the International Commission for Geographical Pathology has pointed out, to syphilitic disease of the liver. Excluding cases which belong to that form of cirrhosis caused by parasitic infection, we are left with a residue of unknown ætiology which resemble the cirrhosis of Lænnec. It has by no means yet been settled whether and to what extent malaria may be a factor in this process. Oudendal and other Dutch observers believe that the condition arises from chronic intoxication in a liver deprived of glycogen by undernourishment and starvation. The clinical picture does not differ from that seen in Europe. Megaw connects hepatic cirrhosis in India with chronic bacillary dysentery, and it possibly is due to chronic absorption of toxins from the large intestine (*see* p. 506).

Diseases of the Gall-Bladder

The rarity of *cholecystitis* in native races is a striking fact. As the Editor has pointed out, there appears to be no direct connection between intestinal dysenteric infection and inflammation of the gall-bladder, nor is there any predisposition to *cholelithiasis*. De Langen and Lichtenstein report that among 150,000 out-patients in Batavia they were only able to make a diagnosis of gall-stones once, and among 422,943 patients thirty times. Intrahepatic cholesterin stones, however, appear to be not infrequent.

Diseases of the Blood

Chlorosis, which has practically disappeared from medical practice in Europe, is probably akin to the *hypochromic microcytic dietetic*

anæmias of the tropics which are such a frequent accompaniment of subnutrition (*see* p. 30). This condition is seen espeially in young native girls in the first year after the onset of katamenia. The anæmia lends a peculiar dull green colour to the countenance which is masked by the pigmentation of the skin. Lymphatic leukæmia and splenomedullary leucocythæmia appear to be met with as frequently as in Europe. The subject of sickle-cell and macrocytic anæmias is dealt with on p. 38.

The position of *pernicious* (*Addisonian*) *anæmia* is by no means so well defined. It is very difficult to get to the truth of the matter, but the anæmia is so akin to that of sprue that the two are very difficult to differentiate. The Editor has records of only three genuine cases (without sprue symptoms) in Indian patients. De Langen and Lichtenstein assert that they have never seen it in the course of their extensive experience in Java. In Ceylon it is given as occurring in 0·3 per 100,000 of the population, and it also appears to be rare in Japan. It is said that in Central Africa no cases are met with in negro races, though Tanganyika appears to be the exception. It must be confessed that it is very difficult to make a diagnosis of genuine pernicious anæmia in natives who are also infected with intestinal parasites.

Diseases of the Heart and Blood-vessels

As *rheumatic fever* is a rare disease in the tropics, rheumatic affections of the valves of the heart are correspondingly rare, so that valvular heart disease is usually syphilitic in origin. Mitral murmurs are seldom heard, and presystolic murmurs are rarer still. The Editor has noted mitral stenosis only once, and mitral regurgitation three times among Indians—lascars in London.

Williams (1938) in Uganda found that syphilis accounted for 53 out of 94 cases of heart disease and is five times as frequent as any other condition; aortic syphilis (aortic regurgitation) was found in 86 out of 894 post-mortem examinations. The average age of onset of symptoms in syphilitic heart disease in natives is forty-one years, i.e., considerably earlier in life than in Europeans. Macfie and Ingram (1920) found cardiac aneurysm very frequent on the Gold Coast.

This is clearly a subject upon which much more precise information is required. W. T. James has never seen a case in twenty-four years' practice in Panama, and J. T. Clarke in a series of 150,000 patients in Malaya had the same experience. That rheumatic infection does occasionally occur even in Central Africa has been shown by Chesterman, who has seen typical rheumatic hearts at autopsy on the Congo. The myocardium is frequently affected in anæmic states. Sclerosis of the coronary vessels appears in normal frequency with advancing age, as in Europeans, but it is a curious fact that the clinical syndrome of angina pectoris is usually absent. It was formerly believed that arterio-sclerosis was peculiar to the educated European classes, but

this does not by any means appear to be the case. Researches of recent years indicate that whenever the age of the subjects is taken into consideration there is practically no difference to be observed in respect of vascular changes, which are at least as common in warmer countries as in the colder. Malignant hypertension (hyperpiesia) appears to be practically absent in poorer natives living on a carbohydrate dietary, though in those who have adopted European habits it is as frequent as it is elsewhere. It should be observed in this connection that the normal blood-pressure in natives in the tropics is per 10–15 mm. of mercury lower than the accepted normal in Europe. In those suffering from subnutrition, it is lower still.

Diseases of the Kidney and Genito-urinary Tract

Vesical and *renal calculi* are amongst the most common conditions encountered in the tropics, the former being the more frequent, especially among boys and young men. Little is known as to their exact causation. By some the explanation is thought to lie in the high concentration of the urine, by others in an unbalanced dietary with consequent lack of vitamin A. Urinary calculi are specially common in south China. In those places (Africa), where urinary bilharziasis is common, the eggs of *Bilharzia hæmatobia* frequently form the nucleus of calculi.

Acute nephritis is commonly encountered, and is attributed to intoxication. De Langen remarks upon its frequency, especially in conjunction with scabies and with superadded septic infections. The clinical picture of contracted kidney with accompanying cardiac hypertrophy and hyperpiesia is rarely seen in indigenous natives, but in those who have adopted European habits, and in Chinese and Europeans in the tropics, it appears to be as common as elsewhere. The rarity of granular kidney is possibly correlated to the simpler diet and its low protein content.

The clinical picture of *nephrosis* (F. von Müller) is frequently seen. It is characterized by extensive and widespread œdema, and a high, but usually variable, albuminuria. There is a low total protein in the blood, and an inverted albumin-globulin ratio with an increased cholesterinæmia. The urea and residual nitrogen are unchanged, whilst the blood-pressure remains normal without effect upon the heart. Nephrosis has often a syphilitic basis, and may be seen together with *quartan* and *subtertian* malaria (*see* p. 76). When all the causes are considered, there still remains a considerable proportion of cases without ascertainable ætiological basis, though many are found in association with ancylostomiasis.

Gonorrhœa, with its accompaniments, is one of the most common and widespread infections throughout the tropics. No one can estimate the extent of its prevalence or the disability that it causes. Not only is it responsible for joint and eye affections, but also for much serious

disease of the female genitalia. Blacklock, for instance, in a thorough medical survey of Sierra Leone in 1930, estimates that 50 per cent. of males over fourteen have active signs and symptoms of this infection.

Diabetes and Glycosuria

It has long been believed that true diabetes (*diabetes mellitus*) is very common in all parts of the tropics. This opinion is based mainly upon the large proportion of carbohydrates consumed. The fact is that the discovery of sugar (or substances which reduce Fehling's and Benedict's reagents) in the tropics amongst the Europeans and better-class natives is comparatively commonly made, but seldom in natives of the poorer class. De Langen, for instance, states that the incidence of diabetes in the Javanese is about 1 in 11,000, i.e., less than 0·01 per cent.

In British India the same appears to be the rule, and diabetes is found among the richer people. It has been pointed out that its comparative rarity in poorer natives is possibly to be ascribed to their shorter expectation of life. Diabetes usually develops in patients of riper years—those over fifty years of age—and this age factor may play a considerable part in statistical records. The relationship between obesity and diabetes is probably also important. Obesity is seldom seen in the average native, but among the rich, who can indulge more freely in the pleasures of the table, a relatively higher incidence of diabetes is observed.

The large number of cases of *benign glycosuria* to be met with in the tropics is remarkable, and these include the condition known as "renal diabetes." In this condition the blood-sugar content should not rise above normal. Patients with benign glycosuria feel perfectly well and show none of the usual symptoms of diabetes. The outlook in renal diabetes is favourable and in no way influences the expectation of life.

General Diseases

Gout.—It has always been held that a close connection exists between gout, obesity and overeating. It is also agreed that during the last half-century the incidence of this disease has almost everywhere decreased. It is always assumed that gout is very rare, or indeed non-existent, among tropical natives. Certainly it is seldom, if ever, observed in primitive peoples, and then only in those who have adopted European habits and customs. The Mahomedans suffer occasionally, while the Hindoos are said to escape entirely. In Manson's time gout was an extremely rare disease in China, and in his diary he recorded one instance of concretions in a Chinaman as an event of great importance. De Langen states that it has occasionally been observed in Java and the East Indies, but records of its occurrence in British India and in Central Africa are quite exceptional. Gout is said to be

unknown in Egypt and in all the countries along the northern shores of Africa.

Arthritis.—Arthritis, which term is used to include the infective and rheumatoid forms, occurs in native races, but to nothing like the same extent as in Europeans in temperate climates. Exact figures are very difficult to procure, as it is necessarily extremely difficult to exclude arthritis of gonorrhœal origin, which is almost universal. The available information has been included by McKinley in a table which purports to give the relative figures of incidence in various tropical and subtropical countries. It is a matter for question whether the figures can be considered really reliable. In Ceylon, for instance, the number reported annually is given as 4,029, and the figure of 2,328 for the whole of India can hardly be considered accurate.

Acute articular rheumatism.—This condition apparently exists all over the world, but it occurs very infrequently in native races, especially where the climate is hot and dry ; consequently the incidence of rheumatic valvular disease of the heart is correspondingly rare. There are those who state that they have never seen rheumatic fever or endocarditis in a lifelong experience in India, Malaya, south China and Central Africa. Thus, Mackinnon states that chorea is never seen in East African children. We have the evidence of Chesterman, however, that it does occasionally occur. Although acute rheumatism has been noted with normal frequency in European residents it is difficult to obtain more accurate information than the meagre data available.

Diseases of the Respiratory System

Tuberculosis.—It has gradually been recognized that the extent of tuberculosis in the tropics is much greater than was formerly thought possible. The rapidity of its spread and the malignancy of the course of pulmonary tuberculosis when first introduced into the Pacific Islands, have been fully realized, and are well described by Robert Louis Stevenson in the case of the Marquesans. Similar disasters have occurred in Samoa, Tonga and other Pacific Islands. In India, Rogers (1919) found that no less than 9 per cent. of deaths are due to tuberculosis, and Megaw estimates that, in the whole of that country, two million people are suffering from it. Scott has drawn attention to the pathological peculiarities of tuberculosis in southern China. It has proved to be the main cause of death in Jamaica, the Gold Coast, the Philippines, on the Congo, and in Tanganyika, where it has been studied by Wilcocks.

For the rapid spread of the disease, its virulent nature, and the poor resistance offered by primitive peoples, several factors are responsible. Usually cases do not come for medical treatment till they are in an advanced stage. The sputum is loaded with bacilli and, living as they do in primitive huts or houses crowded together, infected natives are a constant source of danger to their fellows.

Spitting is a universal habit, and the undernutrition and coexisting malarial and parasitic infections render them all the more susceptible.

The most important factor in the epidemiology of tropical tuberculosis is contact. The natives are able to resist a first infection but, once the disease has become established, their resistance is low. Scott has shown that during the last ten years there has been an enormous increase in prevalence ; in some cases, as in Nigeria and British Guiana, it has been five- and six-fold.

Unfortunately, tuberculosis is a disease which spreads with civilization, e.g., it was unknown many years ago in the Cameroons and in the southern Sudan. In Hong Kong, Scott, in an average of 4,000 autopsies a year, found marked tuberculosis in 5 per cent., and of these, three-fourths were of children under ten years of age. Causes of tuberculosis among natives may be divided into two types, viz., " *natural* " tuberculosis, characteristic of those not immunized in any way against the disease, as in laboratory animals ; and " *modified* " tuberculosis, a more chronic condition, so called because it is modified by primary infection.

It appears to be generally agreed that hæmoptysis is not a prominent sign of tuberculosis in native children, though extraordinarily frequent in adults. Scott has asserted that however extensive the disease, however large the cavity, he has not seen a case among children where death resulted from hæmorrhage. Spontaneous pneumothorax is noted, but amyloid disease in chronic cases is very rare. Bovine tuberculosis, though it occurs, does not appear to be common.

Pneumonia.—Pneumonia maintains its reputation as " captain of the men of death " in the tropics, especially in those countries with a persisting high humid atmosphere, and it appears that, almost everywhere, it has one of the highest mortality figures. Epidemics are specially liable to occur where native labourers are gathered together in compounds and in mining camps. The cause of the disease is more usually a pneumococcal septicæmia, with little localization in the lungs. The clinical picture—rapid onset, extreme prostration and absence of the sthenic signs and symptoms which characterize the disease in Europeans, and the absence of a termination by crisis—differs very considerably from that seen in temperate zones. All these factors impart a varying clinical picture and confound the newly-arrived doctor on his first contact with medicine in the tropics. The story of pneumonia and its ravages in the Rand Mines and in the copper belt of Northern Rhodesia is familiar to students of this subject. It can now be stated that it is in the treatment of pneumonia in tropical natives that sulphanilamide, especially in the form of M & B 693, appears to be having its greatest triumphs.

Zymotic Diseases

Scarlet fever (scarlatina).—All observers are agreed that scarlet fever is never seen in the tropics, or is very rare. De Langen

asserts that, in the Dutch East Indies, such cases as have been tentatively diagnosed eventually prove to be something else. Fischer and others who have looked for it amongst the Negroes of Central Africa have never found it. Possibly the disease may exist in such a mild state as to be unrecognizable, and the rash may be invisible on a dark skin.

Application of the "Dick" test to a selected number of tribes in Tanganyika showed a certain percentage of positive reactions, but equal only to about one-third of the figure usually observed in Europeans, and the few cases reported from Central Africa have all indeed been among European residents. Bötticher (1934) has compiled a review on this subject; in South America and the West Indies, on the other hand, the disease occurs in sporadic outbreaks. In India, too, it is known, though rare; it is of a mild type and is specially liable to attack small children. According to Megaw and das Gupta, from 1923 to 1926 scarlet fever was reported from 212 districts, but of these cases nearly all were European residents. Scarlet fever is common in north China, though it does not occur in the south. Zöller (1925) found that the Dick test gave uniformly negative results.

Measles.—Measles is widespread throughout all tropical countries and runs the same course as elsewhere, and the malignant type is not uncommon. Where no inherent immunity towards the virus existed, as in the case of the Pacific Islands (especially Fiji and Rotumah), a measles epidemic may cause a high mortality in adults as well as children; thus in 1874 over 25,000 Fijians died from the disease. The measles rash has to be distinguished from that of typhus and dengue.

Diphtheria. Diphtheria appears to be widespread and occurs in epidemic form, often when least expected. It is a disease of civilization and is evident only in towns and centres of population. It therefore figures as a feature in the epidemiological statistics of most countries, with the exception of Africa. Whereas it is common in the northern and southern subtropical portions, it is apparently very rare in the tropical zone, and even at the present day in East Africa, Uganda, Tanganyika and in West Africa sporadic cases only are discovered.

Diseases of the Central Nervous System

Syphilitic diseases of the central nervous system, such as tabes and general paresis, are seldom observed in native races and this observation has been made the subject of much comment.

Epidemic *encephalitis lethargica* (Economo's disease) has been noted in epidemics in Sarawak and in Cochin China (Bonnaire).

Epidemics of *anterior poliomyelitis* (infantile paralysis) occur in most tropical countries, notably in Kenya and Uganda, so that contact infections are by no means infrequent in Europeans.

Cerebrospinal meningitis occurs often in large epidemics, especially in the southern Sudan, where it has been shown that the therapeutic application of M & B 693 has achieved remarkable results.

Goitre

Simple parenchymatous or *colloid goitre* is extremely common in Egypt, in the Nile Valley, Sierra Leone, in the Caji districts of the French Congo, and in the Ouelle and Katanga districts of the Belgian Congo. It has been reported in the Dutch East Indies, especially in the Island of Bali. In India it is most common in the Himalayan and subhimalayan regions and in the parts drained by the great Indian rivers (McCarrison), as well as in the western provinces of China. Disorders of secretion resulting in exophthalmic goitre, myxœdema or cretinism are almost unknown.

It has been remarked that goitre is not found among the Bedouin or other desert tribes. In endemic goitre districts iodine should be given to all girls between the ages of eleven and sixteen and to all pregnant women.

Malignant Growths

There is no truth in the oft-quoted popular statement that malignant growths are unknown, or are very infrequent, among primitive peoples. The truth probably is that age-for-age they are as frequent as in civilized communities. The absence of accurate vital statistics, age records, or even registers of births and deaths, make such a comparison at the present moment difficult. There are, however, certain features of malignant disease amongst natives which must be discussed here.

The outstanding facts about malignant growths in the tropics may be stated categorically as follows:

(1) The prevalence of primary liver carcinoma (12 per cent. of all carcinomata, Vint; *see* p. 43); in 90 per cent. of cases grafted upon cirrhosis (Snijders). (Cazanove in French West Africa, Snijders and Straub in Sumatra, Strachan in South Africa, Smith and Elmes in East Africa, French observers in Dakar, Senegal.)
(2) The infrequency of gastric carcinoma.
(3) The prevalence of malignant tumours on the sides of the neck.
(4) The prevalence of skin carcinoma on legs and feet (grafted on chronic ulceration).

Many observers in recent years, especially Snijders, Straub and de Langen in the Dutch East Indies, Vint in East Africa and Rogers in India, have drawn attention to the fact that cancer should not be regarded as formerly, as necessarily being the scourge of civilization. Nor is it correct to state that the number of sufferers from this fell disease is increasing at a staggering rate. It was Hoffman, in compiling statistics for the United States Prudential Societies, who stated that the cancer rate was eight times as high amongst the 500 million of the civilized races as among the 1,200 million uncivilized, including India; but Rogers's statistics, based upon 1,600 post-mortems in Calcutta,

critically arrayed, showed no greater incidence of cancer in England than in India. The carcinomata were equally divided between the squamous and glandular epithelial forms, but the frequency of epitheliomata of the jaws in Calcutta is commented upon, and the same has been noted by French observers in Dakar, Senegal.

Malignant tumours, including both connective tissue and epithelial types, are about equally common in Bengal and in England, with a slight excess in the tropical country ; but both innocent and malignant connective-tissue tumours are considerably more common in Bengal than in England. Vint has shown that, as far as Central Africa is concerned, there is close agreement between figures for malignant disease in natives both in Nigeria and in Kenya. The large number of squamous-celled cancers in the latter country is due to malignant changes in chronic tropical ulcers of the legs, and to epitheliomata associated with this condition.

Carcinoma of the œsophagus is said to be especially common among the Chinese.

A further peculiarity which has recently come to light is the relatively high proportion of sarcomatous to carcinomatous growths. In the extensive series of 5,000 autopsies from the Dutch East Indies, malignant growths were found in 9 per cent., and the proportion of sarcomatous to cancerous tumours was 1 : 3·9, whereas in Europe and America it is 1 : 10.

Sarcomata of the very malignant round-celled type greatly predominate. The clinical course of malignant growths differs, as a rule, between natives and Europeans. Through ignorance or fatalism, patients resist to the very end before asking for medical aid, and are in a hopeless condition when discovered. Malignant disease of the breast is not uncommon in the East African native, and according to Vint, in almost 20 per cent. of cases it is found in males. Sequeira and Vint have pointed out that malignant melanoma, next to squamous-celled cancer, is the commonest form of malignant disease in the natives of East and Central Africa, and O'Connor has stated that in Bengal melanotic sarcoma is distinctly commoner than in Europe. Most of the tumours are found on the foot, and the majority are on the plantar surface. Trauma is the most probable cause, as both sexes walk barefoot, and in a few instances " crab yaws " is an antecedent. The disease is usually locally malignant.

There still remain certain other peculiarities, consequent on local habits and customs. Thus Spittel, Davidson and Turner have shown that cancer (epithelioma) of the cheek is the commonest malignant growth in Ceylon, and is as frequent in women as in men between the ages of thirty-five and fifty ; here, no doubt, it is due to irritation caused by betel chewing. In Travancore, south India, it is also common, so that out of 1,700 cases collected by Bentall it formed 70 per cent.

Kangri-burn cancer is mainly found in Kashmir and is encountered in the older men. In the Mission Hospital there no less than 84 per

cent. of the operations performed are for this condition. Kangri is an earthenware bowl 5–6 in. in diameter, surrounded by basket-work and surmounted by a wicker handle. It is heated by wood charcoal, and is worn against the skin under a loose garment. The growths are commonly found on the inner side of the thighs and anterior surface of the abdomen, above or below the umbilicus. The heat given out by the kangri is estimated at 150–200° F. The growths usually commence in the scars of previous burns. There are no metastases.

Burrows, Molesworth, and many other observers in Australia, have drawn attention to *epitheliomata of the face, especially in Scottish* and Irish immigrants, which is said to be due to excessive irradiation by ultra-violet rays of the sun.

Section I.—FEVERS

Subsection A.—FEVERS CAUSED BY BLOOD PROTOZOA

CHAPTER III

MALARIA

Definition.—The term malaria is applied to certain fevers which are produced by protozoan parasites belonging zoologically to the class Sporozoa. These parasites are peculiar to man, who constitutes their intermediary host and in whose red blood-corpuscles they live and multiply, and may give rise to a periodic fever associated with anaemia, enlargement of the spleen, and the deposit of black pigment in that organ and elsewhere. As a rule the disease is amenable to quinine, plasmoquine and atebrin. Malaria heads the list of diseases in most of the Crown Colonies and in India; indeed, Sinton estimates that, directly or indirectly, it is responsible for at least two million deaths a year in that country and that the economic loss from malaria approximates sixty-seven and a half million pounds per annum.

History.—Meckel discovered the characteristic malarial pigment in the viscera in 1847. On November 6, 1880, at Constantine in Algeria, Laveran first saw the malaria parasite. Fourteen years later, in 1894, Manson formulated his mosquito-malaria hypothesis, basing his argument on facts previously observed in tracing the life-history of the filaria. From 1895 to 1898 Ronald Ross worked upon this theory, conjecturing that some species of mosquito removed the malaria parasite from the blood of man, so that in 1897 he proved that in certain dapple-winged mosquitoes (*Anopheles stephensi*) growing malaria parasites containing pigment were found in the stomach wall. Early the next year (1898) he demonstrated the whole life-cycle of the allied parasite of birds (*Plasmodium præcox*) within the stomach of the appropriate mosquito (Culex), with the production of sporozoites and their entry into the salivary glands. The infection was conveyed from one bird to another by the mosquito *in the act of biting*. Subsequently, Grassi, in Rome, demonstrated that the same cycle of development took place in the case of human malaria parasites in *Anopheles maculipennis*.

Finally, Manson instituted two experiments which disposed of any remaining doubts as to the validity of the theory by arranging for volunteers (Dr. Sambon, Dr. Carmichael Low and Signor Terzi) to live during the three most malarial months of 1900 at Ostia in the Roman Campagna in a mosquito-proof hut; they remained there free from infection. At the same time mosquitoes which had been fed on tertian malaria patients in Rome were

forwarded to London, where they were set to bite the late Dr. P. Thurburn Manson and Mr. George Warren. Shortly afterwards both subjects developed characteristic malarial fever and malarial parasites were found in their blood. Neither of them had ever been abroad or had been otherwise exposed to malarial influences.

Geographical distribution.—An adequate comprehension of the distribution of malaria entails a knowledge of the four different parasites which cause this disease and the associated fevers. The parasites of malaria are known as the *benign tertian, ovale tertian, quartan,* and *subtertian.*

Benign tertian malaria.—The parasite which causes this fever has a distribution that extends far beyond the tropics and subtropics, although at the present day it is found most abundantly in warm countries. Its most northerly range is 60° N., for indigenous malaria has been recorded from Lake Ladoga in Russia and from Southern Sweden. It is known that in recent historical times severe epidemics have occurred in Denmark and Northern Germany, while under the name of ague or "marsh" fever it occurred until recently to a very limited extent in Southern England. This malaria is still prevalent in a mild form in Holland and in the Emden district of Germany in Friesland, where the carrier is *Anopheles maculipennis,* var. *atroparvus.* In America it is prevalent in the valley of the Sacramento at 40° N.

The southern geographical extension is more limited. It occurs, though rarely, in Southern Queensland at 20° S., and in Natal at 30° S. In South America it extends down to 40° S., that is, to the southern limits of Argentina.

As regards altitude, this form of malaria has seldom been recorded, as an indigenous infection, above 6,000 feet. In the tropics themselves it is widespread, but there are certain malaria-free islands which are of great epidemiological interest. These are Barbados[1] in the Atlantic, Tahiti, Hawaii, Fiji, Samoa, and other Pacific islands which are situated at some considerable distance from the mainland, and where it is known that the anopheles mosquito does not occur; there are, of course, other groups, such as the Solomons and New Hebrides, situated in close proximity, where this mosquito abounds, and malaria is rife. Until comparatively recently, Mauritius and Réunion in the Indian Ocean were also malaria-free, but they are now fever-ridden owing to the introduction of anopheles from Madagascar. As a rule, infections of benign tertian malaria, in warm countries where seasonal variations of temperature occur, take place in the early spring or summer, due probably, as Wenyon has pointed out, to the fact that the gametocytes of this parasite can lie latent in the blood of infected persons during the winter months,

[1] Unfortunately malaria broke out in this island in the autumn of 1927 through the introduction of *Anopheles albimanus* which soon became established in suitable pools, but has now been extirpated.

and also that the sporozoites of the malarial infection can survive in infected hibernating anopheles mosquitoes.

Ovale tertian malaria.—Since 1922 it has been suspected that a new variety of the malaria parasite was responsible for a proportion of mild forms of "tertian fever." The parasite of this fever was identified by Stephens as *Plasmodium ovale* (*see* page 881). The fever produced by this parasite usually runs a particularly mild course, has a tertian periodicity, and has so far been reported from Sierra Leone, the Gold Coast, the Congo, Nigeria and Uganda, and recently one authentic case has been found in Eastern Russia. It is liable to be confused with quartan malaria.

Quartan malaria.—As compared with the benign and subtertian forms of malaria, quartan is rare. The infection, however, can persist much longer than can the other forms—according to Mühlens, as long as nineteen years. Until recently, it appears to have been commoner in temperate latitudes than in the tropics. It has been noted in Central Europe, but in the tropics themselves it is quite unknown in some highly malarious places, and it has a peculiar patchy distribution in the Mediterranean area, in Macedonia, Palestine, Iraq, southern India, and the Andaman Islands, and is the dominant form in certain districts of Ceylon and the Malay States. It occurs in New Guinea and adjacent islands. In Africa it is found sparingly in the central tropical belt from Kenya Colony to Sierra Leone. In the New World it is relatively rare in the West India Islands, though common in Antigua. It is found in Panama and Brazil.

The general statement that quartan fever is more a disease of the subtropics than of the true tropics, but that in both it has a very limited topographical distribution, probably expresses the truth. In Macedonia and in the regions south-west of the Caspian, the maximum incidence of quartan malaria occurs during the months July to September; but it was noted during the Great War that the infection remained almost entirely confined to the children of the native villages and did not spread to the troops, who were quartered in the vicinity for over three years. This is a feature of the quartan parasite which requires further investigation.

Subtertian malaria is confined to the warmer regions of the earth, and to the more intensely malarial districts in these; hence the name "tropical" which has been applied to this type of infection. Its limits correspond to a mean summer isotherm of 70° F., and a mean winter isotherm of 48° F. In Europe it is therefore rare, except in such highly malarious centres as Salonika and the Danube marshes; but in the tropics, wherever fever is popularly regarded as being peculiarly virulent, the subtertian parasite is common. Like the quartan parasite, it has a patchy distribution, especially in hot, dry, desert countries with a limited water supply. In the oases of Northern Africa it is the commonest form. The same may be said of West Africa, Asia Minor, and in fact the greater part of the tropics. About

the year 1920, subtertian malaria was imported into Central Russia by refugees from Turkestan, and spread as far north as Moscow, where fresh cases occurred even in the winter season.

In Cairo, Biggam has shown that numerous cases of subtertian malaria of a particularly malignant type were due to indiscriminate intravenous injections of heroin among drug addicts. This, of course, was brought about by the use of unsterilized hypodermic syringes, in which a little blood is usually sucked up prior to the inoculation to ensure that the needle has entered the vein. This interesting development has been confirmed by Appelbaum and Gelfand in New York (1934), where they found 39 drug addicts, admitted to the Bellevue Hospital, suffering from malaria. The drug—diacetyl morphine—had been administered by the intravenous route. In ten cases specially studied the parasite was quartan in three; in the remaining seven it was subtertian. Boyd and Schlackman find that the mortality rate among these drug addicts is much higher than the ordinary rate. The condition may resemble diabetic coma, insulin shock or various neurological conditions.

In the subtropical zones it occurs as a primary infection in late summer or early autumn; hence the synonym *æstivo-autumnal fever*. This peculiarity, as regards seasonal and geographical distribution, may be explained by the fact that, for its development in the mosquito, the subtertian parasite requires a higher atmospheric temperature than suffices for the quartan and tertian parasites. Hence, although the benign and the subtertian parasites are generally found associated together, and the latter can be acquired at any time in the tropics, it is only in the summer or autumn that it can be acquired in the subtropics and more temperate zones. It has been proved that if the atmospheric temperature falls below 15° C., the development of the oöcyst in the mosquito is arrested. On the other hand, when once the sporozoites have entered the salivary glands of anopheles, they are capable of infecting man with the parasite even during the winter season.

Epidemiology and endemiology of malaria.—In considering the epidemiology of malaria, two things must be carefully distinguished: The circumstances leading to the invasion of the human body by the malaria parasite; and the circumstances favouring the clinical manifestation of such invasion.

(1) *Circumstances leading to the invasion of the human body by the malaria parasite.*—Whatever favours the presence and increase of the malaria-bearing species of mosquito tends to the increase of malaria, and vice versa; whatever favours the access of these insects, and the parasites which have passed into them, to the human body favours the acquisition of malaria.

The modern conception of the spread of malaria is intimately related to the susceptibility of the human host. It is again the old problem of the seed and the soil. It has been abundantly shown that when the health is unimpaired, there is increased resistance to

malarial infection, but when the constitution has been undermined by over-exertion and under-nourishment, and the physical resistance has been diminished by co-existing disease, such as tuberculosis, dysentery, and ancylostomiasis, then the infection is apt to spread more rapidly and to assume particularly virulent and intractable forms.

The strip of flat, waterlogged country lying along the foot of mountain ranges, the deltas of large rivers, the pool-dotted beds of dried-up streams, areas of country which have fallen out of cultivation, recently deforested lands, are, in many instances, notoriously malarial. Well-drained uplands and carefully cultivated districts are, as a rule, healthy. There are, nevertheless, instances of elevated, arid, and sandy plains which, under certain hydraulic conditions, are intensely malarial. Towns, as a rule, are much less malarial than villages or the open country.

These circumstances evidently have reference to the distribution of species of anopheles mosquitoes. Like other insects, mosquitoes occasionally, under specially favourable conditions, increase enormously in numbers and spread out in every direction. New species, which may belong to the malaria-bearing kinds, may be introduced into places where they formerly did not exist. Thus it is believed that a mosquito capable of subserving the malaria parasite was introduced in this way in the early sixties into Mauritius, an island whose fauna and flora had been hitherto very peculiar and special, and the same thing appears to have happened in Barbados since 1927.

Wenyon explains the seasonal variations of the two dominant forms of malaria as observed in Macedonia and Palestine by the fact that the benign tertian type of infection tends to relapse over a long period and is more resistant to quinine, while in the subtertian, though the individual attack may be more severe, the cases are more amenable to treatment and there is little tendency for the infections to persist from one season to the next. At the height of the malaria season the numbers of benign and subtertian cases may be approximately equal, but the latter develops much more rapidly into a heavy infection and produces in a shorter time a greater number of gametocytes. Thus subtertian malaria tends to spread in epidemic form with greater rapidity, which is characteristic of these autumn epidemics, at a time when conditions are favourable. There is no evidence that any particular species of anopheline mosquito is especially associated with one type of malaria.

Sayers has pointed out a fact, which has also been observed elsewhere, especially by Wenyon in Salonika, that in the Western Solomon Islands the commonest type of malaria parasite in children between two and ten years of age is the quartan, and after that age it is seldom met with. The incidence of benign tertian malaria is highest in children under one year of age, whilst, in the Solomons, at any rate, the malaria of adults is practically all subtertian.

According to Bagster Wilson malaria causes comparatively little illness among the Bantus in Tanganyika, though this is an area of high endemicity and *all* babies are infected with malaria *(P. falciparum)* before they are five months old. The immunity which can be acquired

in respect of this parasite is less than in the case of other species, especially *P. ovale*.

One of the most important conditions necessary to the sporogonic phase (p. 60) of the malaria parasite is a sustained average temperature of at least 60° F., and a humidity of at least 63 per cent. (Gill). The malaria parasite will not develop in the mosquito at low temperatures, but, when once infected, the anopheles is capable of conveying the disease at very low temperatures indeed. Altitude *per se* has, apparently, no influence on malaria. It is the decrease in temperature usually implied by an increase in altitude that is the real determining circumstance in bringing about a diminution in the prevalence of malaria in uplands.

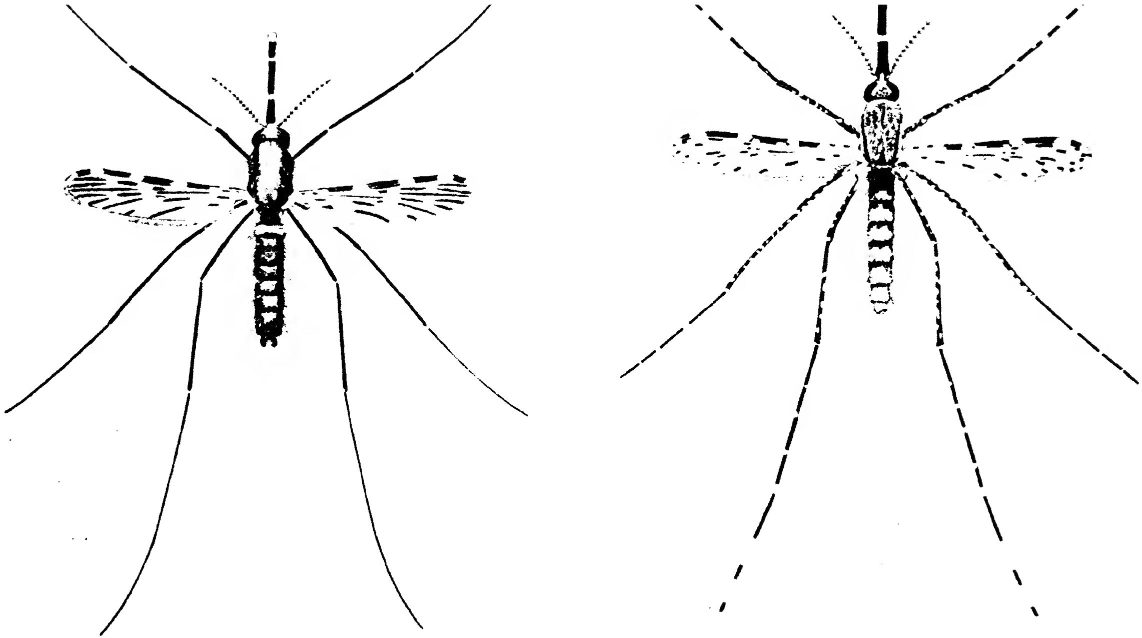
It is doubtful whether the malarial mosquito can be transported very far from its native pool. Generally speaking, some thousand or fifteen hundred yards of water between a ship and a malarious coast may suffice to secure immunity to the crew. Climate definitely limits the spread of malaria. The diffusion of malaria by wind plays a minor part. Kligler, in Palestine, finds that the flight of anopheles can be classified in three grades—direct flight about 1½ miles; range of dispersion during the breeding season 3½ kilometres; but during the hibernation flight it may be as much as 8 kilometres. The intervention of a belt of trees between a malarial swamp and a village is said to protect from malaria the houses on the leeward side of the trees. The trees may filter out the mosquitoes by affording them protection from winds. Open windows and doors, by giving access to mosquitoes, are sources of danger in malarious countries; for this and similar reasons, sleeping on the ground, on the ground floor, or unprotected by a mosquito-curtain, is dangerous.

Based evidently on the observed habits of the mosquito, there is a belief that the times just before sunrise and just after sunset, and the night, are most dangerous as regards liability to contract the infection. Although mosquitoes are most active during twilight and night, they bite readily enough during the daytime in shady and windless places, as in thick jungle or in a dark room. A very few species are diurnal in habit. (Plate II.)

(2) *Circumstances favouring the clinical manifestation of malarial invasion.*—As a rule, a successful malarial infection declares itself within a week or ten days. As with other infections, certain individuals resist the pathogenic influences of the malaria parasite for a longer period. A very few appear to be permanently immune. Everything tending to cause physiological depression favours susceptibility and acute manifestations.

A malarial subject, while in the mild climate of the tropics, may keep in fair health; but when he is plunged into the stormy winter of the north, is exposed to cold, and has long watches and fatiguing work, latent malaria will very probably become active and ague follow.

An introduction to the study of mosquitoes will be found on pp. 980–989.



Anopheles culicifacies Giles

Anopheles maculatus Theobald.

TWO MALARIA-CARRYING ANOPHELES. 14.

(*After Christopher's "Fauna of British India"*)

PLATE II

ÆTIOLOGY : GENERAL DESCRIPTION OF THE PARASITES THAT CAUSE MALARIA

The four species of parasites causing malaria in man differ from each other in minor points and in their morphology, but the general course of the life-history is the same for all. As regards man, they exhibit two distinct phases—an intracorporeal and an extracorporeal phase. Each species of parasite has its special **intracorporeal life-cycle,** which may last approximately from forty-eight to seventy-two hours, according to the species.

On examining fresh malarial blood an hour or two before the occurrence of a paroxysm, the parasite is recognized as a pale disc occupying an area within the red blood-corpuscle (Fig. 3, *a*), while scattered throughout the protoplasm are a number of intensely black, or reddish-black particles, which are now known to be excrementitious material called *hæmozoin*. As the parasite matures the hæmozoin

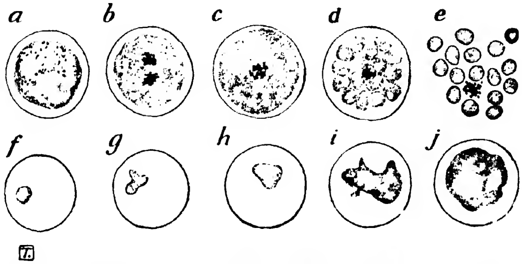


Fig. 3.—Evolution of the tertian parasite, unstained (*see* text).

collects into central blocks, round which the protoplasm of the parasite arranges itself in segments. When this cycle is completed the including corpuscle breaks down and liberates the spherules or spores, none of which contains hæmozoin. A proportion of the spores, escaping phagocytosis, attach themselves to other red blood-corpuscles, which they contrive to enter. In the interior of these newly infected corpuscles the young parasites grow at the expense of the hæmoglobin, and exhibit active amœboid movement. By appropriate staining the free spherules are found to consist of a nucleolus, which is seen to be surrounded by a lightly-tinted covering of protoplasm. As the parasite grows and approaches maturity, the nucleolus enlarges, becomes less defined, and then disperses ; finally, just before sporulation both nucleus and nucleolus cease to be distinguishable (Fig. 4, *a*, *j*).

At this stage these elements become fragmented and diffused throughout the protoplasm. Later, the nuclear elements reappear as numerous minute, scattered nucleoli ; and it is around these that the protoplasm of the segmenting parasite arranges itself to form the spherules (Fig. 4, *b*, *c*). The vesicular character of the nucleus

does not usually appear in the spherules until after these have become free in the liquor sanguinis (Fig. 4, *d*).

The hæmozoin particles, characteristic of the malaria parasite, occur as black or very dark-red dust-like specks, coarse grains, or short rods, either isolated or aggregated into larger or smaller, more or less dense clumps. Until the concentration of hæmozoin which precedes the formation of spherules takes place, the particles are scattered. Apparently, so long as the nucleus remains entire the hæmozoin is peripheral; when segmentation occurs in the nucleus the hæmozoin becomes central.

Extracorporeal or mosquito cycle.—The four species of malaria parasite undergo a similar cycle of development in the body of the mosquito (*see* Appendix, p. 886), but only in mosquitoes of the genus Anopheles.[1]

When fresh malarial blood is examined in a wet preparation shortly

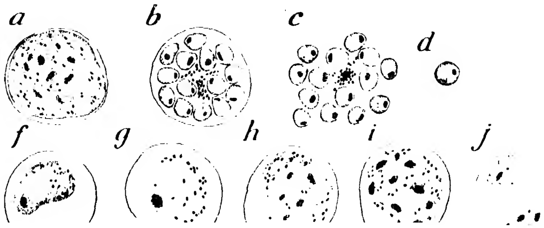


Fig. 4.—Evolution of the tertian parasite, stained (*see* text).

after it has been drawn, what is known as the "flagellated body" may be observed. The flagellated body[2] is derived from the sexual cells or *gametocytes*; *composed of colourless protoplasm and hæmozoin* granules, it floats freely in the liquor sanguinis. The flagella (or more correctly *microgametes*) number from one to six, or more. They are extremely delicate filaments which move about rapidly, and every now and again break away from the parent body and swim about with vibratile movements. These bodies are never seen in the fresh blood, but only when it has been removed from the body and has become chilled in the process. The gametocytes of the four forms of malaria parasite differ in shape (Figs. 5, 6). In the benign tertian, ovale tertian and quartan they are round, while in the subtertian they are crescentic. (For further development in Anopheles, *see* p. 886.)

[1] K. B. Williamson (1937) has claimed that development of benign, subtertian and quartan malaria up to the sporocyst stage can take place in *Culex bitæniorhynchus* in Malaya, but these observations require further confirmation.

[2] The expressions "flagellated body" and "flagellum," applied to this phase of the malaria parasite, though graphic enough, are somewhat misleading. The flagella of the malaria parasite are in no sense analogous to the flagella of the flagellata; they really function as spermatozoa. The proper zoological terms for this and the other phases of the malaria parasites are given at p. 887.

Possibility of a latent phase of the malaria parasite in the human body.—It is a well-established fact that when the fever subsides the parasite disappears from the general circulation, either spontaneously, or as the result of the administration of quinine, atebrin, or plasmoquine. Usually, after an interval of weeks or months, the parasite may reappear in the peripheral blood. So far no satisfactory explanation has been given for this extraordinary latency. In benign tertian and quartan malaria it may be as long as nine

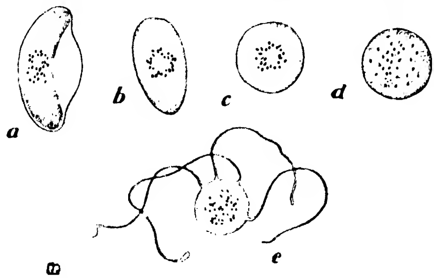


Fig. 5.—Evolution of the flagellated body from the crescent (male gametocyte).

months subsequent to the administration of atebrin or plasmoquine (*see* p. 136). Shute has suggested from this, and from other evidence, that the sporozoites when injected into the skin by the mosquito, do not all reach the blood-stream, but become held up in the skin where they may live for a long period. Only those which enter the blood directly become converted into merozoites and give rise to an immediate attack of fever.

Transmission of the malaria parasite to the fœtus.—Malaria parasites have been demonstrated in the blood of a child before birth (Buckingham), while Heiser has recorded the case of an infant seven days old with crescents of *P. falciparum* in its blood. Congenital malaria is very exceptional, and probably only occurs when accidental tears of the placenta allow passage of parasites from maternal to fœtal circulation. The question is

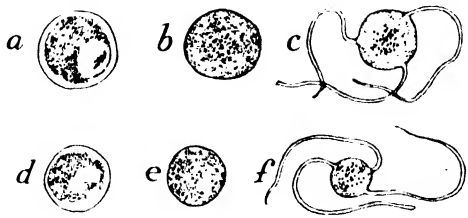


Fig. 6.—*a*, *b*, *c*, Evolution of the flagellated body from the respective gametocytes in tertian fever ; *d*, *e*, *f*, evolution of the flagellated body in quartan fever.

whether methods of transmission exist other than by placental hæmorrhage.

Blacklock and Gordon discovered in Sierra Leone that of pregnant women infected with *P. falciparum*, 36 per cent. sustain intensive infection in the placenta leading to death of the fœtus.

Jean and van Nitsen record eight children either born dead, or dying soon after birth, of whom six showed malarial schizonts in the spleen. Recently undoubted cases of congenital transmission of benign tertian malaria have occurred in London, two months after birth. (Jones and Brown; Hewlett and Tanner.)

Wickramasuriya in Ceylon finds that congenital malaria is a definite clinical entity, and in three out of six proven cases of trans-placental infection the death of the fœtus could be attributed to malaria contracted *in utero*. He has also observed a persistent slight pyrexia in children born of malaria-infected mothers, especially in the case of *P. falciparum*, and which can be attributed to congenital malaria. A physiologically healthy placenta will not permit the passage of parasites from the mother to the fœtus. It is suggested that the malaria infection induces pathological changes in the placenta itself, most probably traumatic tears.

Transmission of malaria by blood-transfusion.—It is now recognized that considerable danger exists in conveying malarial infection by blood-transfusion with citrated and stored blood. This is specially the case with *P. vivax* in the blood of donors who may have been exposed to a malaria infection within a period of four years. Antschlewitsch, in Russia, has shown that in stored citrated blood danger exists up to the eighth day of storage,[1] whilst Thomas, Keys and Dyke have reported upon cases in which this accident has happened in England in cases transfused from an apparently healthy donor. Other Russian workers have found it necessary to add up to 1 gramme of quinine to the litre of blood (Ackermann and Filator).

In France, Harvier, Le Brun and Lafitte have recorded such a case in a donor who had been in Algeria ten years previously; Nobecourt, Liege and others in one who had had malaria seven years before. In London recently a case of fatal quartan malaria has been recorded in a baby transfused with compatible blood from its father who had lived in Ceylon twelve years previously and who had never suffered from any clinical manifestations of malaria (Nabarro and Edward).

The Four Forms of Parasites and their Associated Fevers

There are four clinical types of malarial disease which are associated with four distinct and corresponding species of malaria parasites. These different species have been classified according to (*a*) the duration of their respective life-cycles inside the human body; (*b*) their morphological characters; (*c*) the clinical phenomena to which they give rise; and (*d*) the results of inoculation experiments.

Benign parasites are of three kinds: the *quartan*, which has a cycle of seventy-two hours and causes a fever that recurs every fourth day, counting from the first day of fever—*quartan fever*;

[1] Hutton and Shute have now shown that malaria parasites may survive for days, or even weeks, in blood stored at low temperatures—about 4° C.

TABULAR STATEMENT OF THE CHARACTERS OF THE FOUR SPECIES OF MALARIA PARASITE

	Duration of schizogonic cycle	*Movement*	*Hæmozoin*	*Trophozoites*	*Adult schizont*	*Number of merozoites*	*Form of gametocytes*	*Alterations in corpuscles*	*Relative number of parasites in peripheral and visceral blood*	*Liability to relapse*
1. Benign tertian parasite. *Plasmodium vivax.*	48 hours	Active amœboid	Fine yellowish brown in colour.	Signet rings of various sizes, growing forms irregular in size with vacuole.	Larger than a red cell	14-24 average 18-20.	Round or slightly ovoid larger than the red cell	Hypertrophied and pale, stippled with Schüffner's dots.	Parasites numerous in all parts of the body in various stages of their cycle	Relapses noted up to 3¼ years from time of original infection
2. Quartan parasite, *Plasmodium malariæ.*	72 hours	Slight in immature forms	Coarse, and dark brown.	Signet rings as in *P. vivax* growing forms band-like or angular. Vacuole soon disappears.	Slightly smaller than a red cell	6-12 average 8 or 9	Round or slightly oval, size of red cell.	Not enlarged, may be slightly contracted ; no stippling	As in *P. vivax.*	Infection particularly persistent. Relapses may occur for 6 years or more from time of original infection.
3. Subtertian parasite, *Plasmodium falciparum (Laverania malariæ).*	24-48 hours irregular	Active amœboid	Pigment blacker than in other forms, may be aggregated into coarse granules	Rings small often containing two nuclear granules, and sometimes attached to edges of red cell	Distinctly smaller than a red cell	8-24, sometimes more. Very variable	Crescentic or sausage-shaped.	Usually unaltered. in later stages paler sometimes containing coarse dots or irregular mottling Maurer's dots or clefts.	The greater development of the parasite takes place in the internal organs, hence the relative scarcity of all, save most immature forms, in peripheral blood.	Much less than in other two forms; infection intense in early stages. Relapses rarely occur after 9 months from time of infection. Maximum period observed, 1¼ years.
4. Ovale tertian (*Plasmodium ovale*).	48 hours	Non-amœboid	Blackish brown.	Rings indistinguishable from those of *P. malariæ*	Smaller than a red cell	8-12	Oval, size of red cell	Oval and irregular	As in *P. vivax.*	Short-lived infection.

the *benign tertian* parasite, with a cycle of 48 hours, and causing a fever which recurs every third day, counting in a similar way—*tertian fever* ; and the *ovale tertian* which in many respects resembles the latter.

The malignant or *subtertian* parasite is also known as the *æstivo-autumnal,* and has a life-cycle of approximately 48 hours.

(For characters of the species, *see* accompanying Table.)

INOCULATED OR THERAPEUTIC MALARIA

Following the work of Wagner-Jauregg of Vienna, the treatment of general paralysis of the insane and other grave nervous disorders is now being carried out by the injection, subcutaneously or intramuscularly, of 1 to 2 c.c. of blood containing benign tertian parasites,[1] with the consequent production of attacks of malaria in the person thus

[1] It is most important that *P. vivax* and *P. ovale* strains should be used ; deaths have occurred from inoculation with certain strains of *P. falciparum*, but others in James's hands have proved beneficial. Favourable results have been recorded in Vienna from the employment of the *Spirochæta duttoni* of relapsing fever in place of malaria.

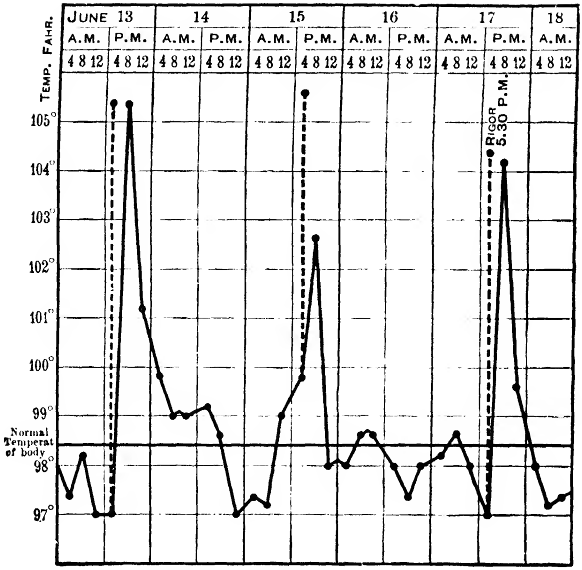


Chart 1.—Benign tertian ague.

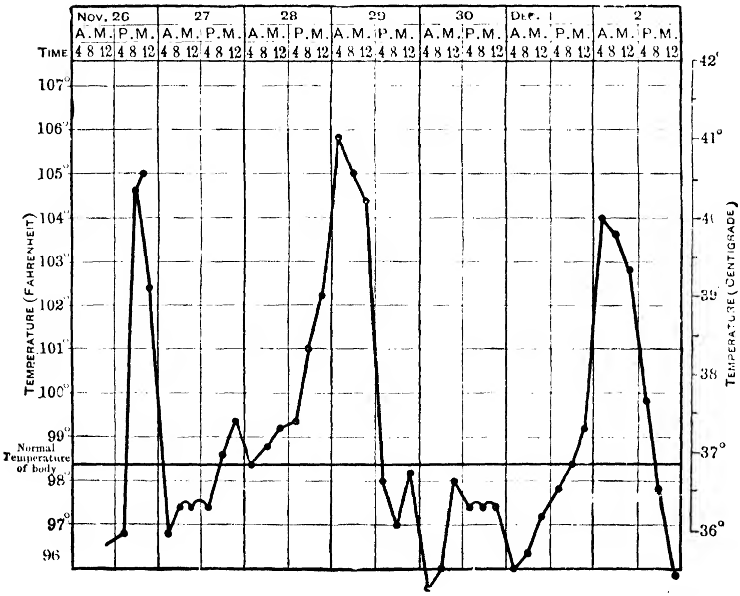


Chart 2.—Quartan ague.

Plate III

MALARIA PARASITES. × 2,000.

A.—Subtertian Parasite (*Plasmodium falciparum*).

Fig. 1.—Subtertian rings. Note the marginal form and, in one, double chromatin dots.

Fig. 2.—Quarter-grown parasite. When seen in the peripheral blood this denotes a severe infection, as it normally occurs in the capillaries of the internal organs. Note discoloration of cell, its irregularity and the pernicious stippling—known also as "Stephens'" and "Christopher's" dots, and also as "Maurer's dots" or clefts.

Fig. 3.—Schizogonic stage, or rosette form, with thirty spores, also usually in capillaries of internal organs—seldom seen in peripheral blood.

Fig. 4.—Male gametocyte (crescent).

Fig. 5.—Female gametocyte (crescent) showing concentration of chromatin and pigment.

B.—Benign Tertian Parasite (*Plasmodium vivax*).

Fig. 1.—Young ring form.

Fig. 2.—Quarter-grown parasite. Note Schüffner's dots and slight enlargement of corpuscle.

Fig. 3.—Half-grown parasite. (Amœboid form.)

Fig. 4.—Three-quarter grown parasite. (Amœboid form.)

Fig. 5.—Presporulating stage showing fragmentation of chromatin.

Fig. 6.—Complete schizogony. (Rosette stage with 20–24 spores.)

Fig. 7.—Male gametocyte. Note loose arrangement of chromatin and purple tinge of protoplasm.

Fig. 8.—Female gametocyte. Note compactness of chromatin and blue tinge of protoplasm.

C.—Quartan Parasite (*Plasmodium malariæ*).

Fig. 1.—Ring form.

Fig. 2.—Quarter-grown parasite ("band form"). Note corpuscle is not enlarged.

Fig. 3.—Half-grown parasite ("band form"). Note the scattered black pigment.

Fig. 4.—Presporulating stage.

Fig. 5.—Complete schizogony. (Rosette stage with 8–9 spores.)

Fig. 6.—Male gametocyte. Note purple tinge of protoplasm with heavy pigmentation.

Fig. 7.—Female gametocyte. Note blue tinge of protoplasm. (Blue dots, when present, are known as Ziemann's stippling.)

Fig. 8.—Normal red blood-corpuscle for comparison of size.

D.—Ovale Tertian Parasite (*Plasmodium ovale*).

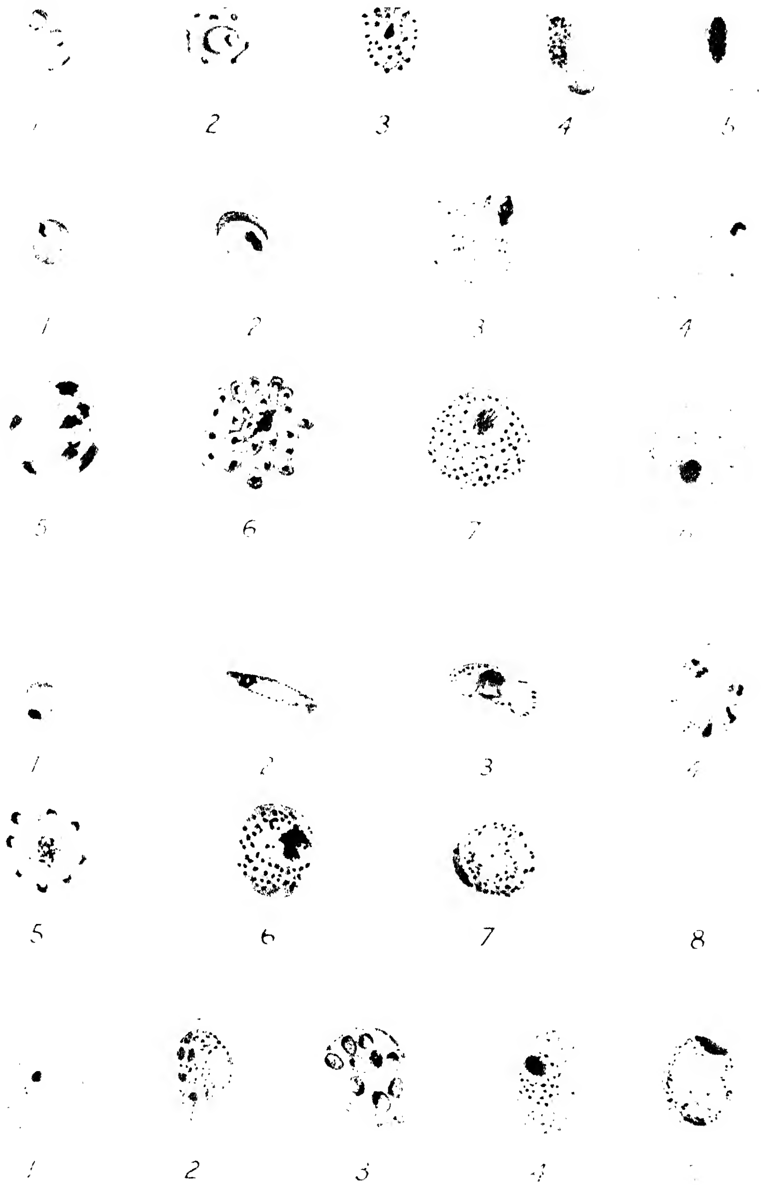
Fig. 1.—Ring form. Note Schüffner's dots.

Fig. 2.—Presporulating stage. Note irregular and oval shape of corpuscle with coarse and prominent Schüffner's dots.

Fig. 3.—Complete schizogony. Note irregular distribution and oval shape of spores and also distortion of corpuscle.

Fig. 4.—Male gametocyte. Note coarse Schüffner's dots and purple tinge of protoplasm.

Fig. 5.—Female gametocyte. Note marginal arrangement of pigment.



MALARIA PARASITES

PLATE III

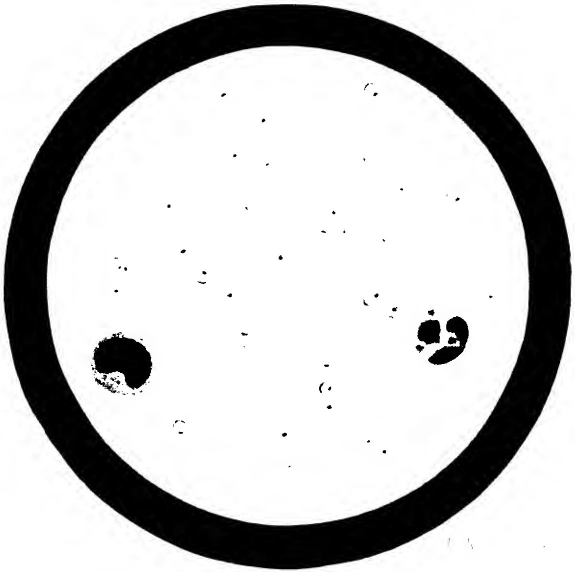


Fig. 1. Blood-film from fatal case of subtertian malaria, showing heavy "ring" infection.

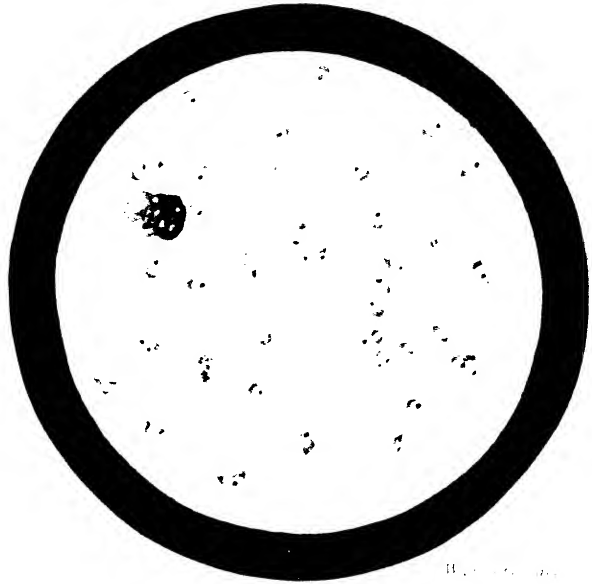


Fig. 2. Thick blood-film preparation of subtertian rings and crescent stained by Leishman to show appearances after dehæmoglobinization. × 1000.

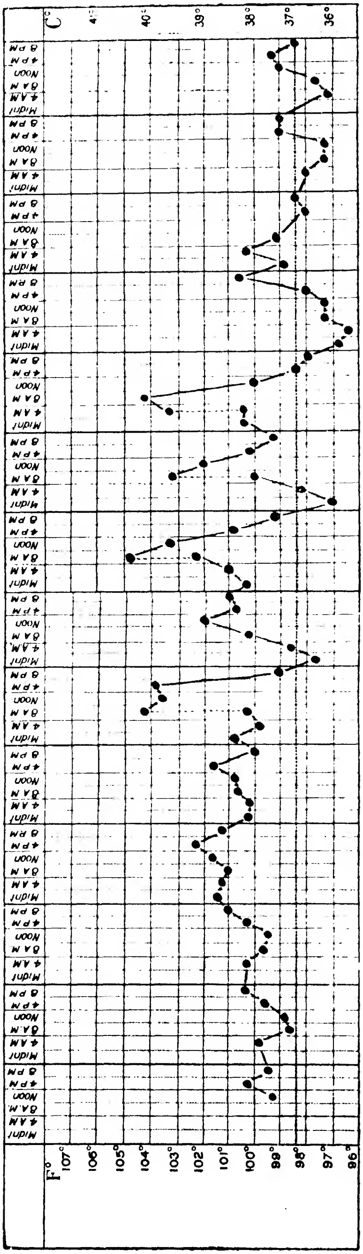
THE BLOOD PICTURE IN SUBTERTIAN MALARIA.

injected. The best results are obtained with blood which has been immediately defibrinated and kept in a thermos flask at freezing-point.

Artificial malaria may also be produced by the bite of an infected mosquito or by the actual subcutaneous injection of the extract of the insect's salivary glands containing sporozoites. Contrary to the opinion formerly held, it has been shown that inoculation of sporozoites from the salivary glands of one infected anopheles will produce in some persons *quotidian* rigors due to parasites sporulating within a day of each other. In many cases, also, after an incubation period of 7–10 days the onset of the malaria attacks is characterized, not by typical intermittent fever, as seen in Charts 1, 2, but by a *remittent fever* which may persist for a week or more before becoming frankly intermittent (Chart 3). This feature appears to have been noted in the historic inoculation experiments originally carried out by Manson and Grassi, to which reference has been made. The results of this form of treatment have, according to Yorke and Macfie, been favourable: 27·4 per cent. of general paralytics were regarded as temporarily cured, while in a further 20·2 per cent. great physical and distinct mental improvement were observed. It has been proved that stabilization takes place so that re-adaptation to family life and social responsibilities is possible. In other forms of cerebrospinal syphilis, it would seem as if malaria therapy acts as a mordant for the specific medication employed.

In inoculated infections disinfection by quinine or atebrin is extraordinarily easy. To effect a complete cure, the amount of quinine administered has varied from 45–150 gr. and 3 grm. of atebrin. Relapses after subcutaneous inoculation of malaria are extremely rare, while in naturally-acquired malaria they are almost the rule. It seems, therefore, that malarial infection produced by the injection of sporozoites is much more long-lived and much less amenable to quinine. Valuable information as to the failure of quinine to act in a prophylactic manner has also by these means been obtained. The administration of quinine in 10-gr.-solution daily for five days previous to, the day of, and eight days after the bite of infective mosquitoes fails to prevent the development of malaria: similar results have been obtained in cases where 30 gr. of the drug in solution were given on the day of feeding infective mosquitoes and on each of the two following days. These experiments show that quinine has no action upon the sporozoites injected by the mosquito: on the other hand the development of malaria can be prevented by 10 gr. of quinine daily taken for ten days after the infecting bites.

Artificial infection of susceptible species of anophelines and technique employed. For the production by mosquito bite of malaria infection in general paralytics, James uses mainly wild-caught insects obtained in a country district where malaria does not occur. The insects are collected one by one in a test-tube and transferred to a mosquito cage. When about 300 have been caught, a waterproof cover is drawn over the cage, which is then taken to the laboratory. After removal of the cover, the cage is placed in an incubator at 23° C. for twenty-four to forty-eight hours in order that the blood in the stomachs of the mosquitoes may be digested quickly and that they may be ready to feed upon the infecting case. For the case to be suitable for infecting mosquitoes it is essential that the peripheral blood should contain male and female gametocytes in the ripe stage; the male forms should "flagellate" readily in a moist-chamber preparation of freshly-drawn blood (*see* p. 1024).



In artificially-inoculated malaria cases, in order to produce, for example, a sufficient number of gametocytes of benign tertian, James finds it best to permit the patient to have a number (ten or more) of attacks of malaria before administering a small dose (5 gr.) of quinine. A remission of fourteen to seventeen days will occur before the next attack, when gametocytes in the right stage will be found abundant in the peripheral blood.

When the mosquitoes are to be fed on the infecting cases they are taken from the cage in a test-tube and then transferred to glass jars. The tops of these jars should be covered with a piece of paper in which a half-circle valve of the same size as the mouth of the test-tube is cut. In order to liberate the mosquitoes the cotton-wool plug is withdrawn from the mouth of the test-tube at the time it is pushed through the valve. When the mosquito has flown into the bottle, the tube should be withdrawn and at the same time the valve should be plugged with cotton-wool. After twenty mosquitoes have been transferred to each of four or five bottles, pieces of mosquito-netting should be laid over the paper which closes their mouths, and by keeping the mosquito-netting in place with the palm of the hand, the paper should be carefully drawn away, thus leaving the netting as a cover, and it should then be tied on tightly.

The jars containing the mosquitoes are then placed on the leg of the patient. An attendant should keep the mouths of the jars pressed closely against the skin during the period allowed for feeding, which is usually about twenty minutes. The mosquitoes bite readily through the netting,

but when they have fed, the jars are placed inside the cage and the netting covers removed, when they escape into the cage. The cage is kept in an incubator at 23° C. (73° F.), and by standing a bowl of water in it and hanging wet cloths, the air is kept as nearly saturated with moisture as is possible. The procedure described is repeated daily, the mosquitoes being fed for at least five days on an infecting case. Afterwards they are fed every day, or every other day, on a patient who is awaiting treatment, in order to ensure that they obtain the necessary amount of nutriment. Some mosquitoes die every day, and these are dissected to ascertain the progress of the malaria infection. When sporozoites are present in the salivary glands (usually between the tenth and fifteenth day after the first infection feed), incubation is discontinued and the group of insects should be kept either at room-temperature or in an icebox at 5° C., when further development will be arrested and the mosquitoes will remain torpid, but ready to infect a patient when required.

In order to infect a patient, four or five mosquitoes are transferred from the cage to one of the glass jars and allowed to bite the patient in the manner already described. Usually two or three bite within a few minutes. When human blood cannot be obtained to nourish the mosquitoes, they can be fed on glucose solution on cotton-wool.

By this method James has shown that nearly 100 per cent. become infective; while the experience of Wenyon in Salonika and that of the Editor in England shows that after a single feed on a suitable benign tertian case fully 80 per cent. of *A. maculipennis* develop oöcysts in their stomachs if the air is kept moist and warm.

Morbid anatomy.—The *spleen* is enlarged—often very much so; its surface is dark—black sometimes—what is called pigmented. On section, the gland tissue is found to be dark also. Generally the parenchyma of the organ is so much softened as to be almost diffluent, so that the tarry pulp can sometimes be washed away by a quite gentle stream of water. In acute and rapidly fatal cases of subtertian malaria the capsule is stretched almost to bursting-point, and resembles a bladder distended with congealed blood. The weight varies enormously according to the duration and intensity of the infection. Clark estimates that of the normal spleen in negroes at 140-160 grm. and believes that it must exceed 300 grm. before it can reasonably be detected by palpation during life. The *liver*, too, is softened, congested, enlarged, and pigmented, and of an olive-brown colour. The vessels of the *pia mater* and *brain cortex* are full, and the grey matter may present a peculiar leaden hue. In fatal subtertian cases of the cerebral type, punctiform hæmorrhages are present in the white matter of the brain, especially in the corpus callosum. These lesions are due in the first instance to blockage of the blood-vessels by the sporulating parasites. Margulis, Thomson and Seyfarth have described malarial granulomata, or focal degenerations, which are direct results of hæmorrhages. In microscopical appearances they somewhat resemble tubercles and they are formed of the conglomeration of glia cells round the centre of degeneration (Fig. 7). Possibly this grave alteration in the structure of the cerebral cortex may be responsible

for the various mental and nervous symptoms which frequently ensue upon an attack of cerebral malaria. The *marrow* of the spongy bones, such as the sternum and the bodies of the vertebræ, is also dark and congested; and a similar state of pigmentation and perhaps congestion may be discovered in the *lungs*, *alimentary canal*, and *kidneys*. In fatal subtertian cases these organs are specially affected, a general parenchymatous degeneration with special incidence on the epithelium of the tubules being present.

The blood.—As the malaria parasite is a blood parasite, we naturally expect that the primary effect of its presence will be exercised on, and manifested in, the blood; and, as the parasite lives in and at the expense of the corpuscles, destroying a certain proportion of them—in fact, all those attacked—we look, in the first instance, for a corresponding diminution in the number of the corpuscles—an oligocythæmia. In order to produce symptoms, it is estimated that there must be at least one parasite to every 100,000 red cells.

The reduction of the red cells in malaria cannot be accounted for by the proportion of the red blood-corpuscles attacked or directly consumed by the parasite. The amount of hæmolysis actually produced by the mechanical action of the parasites should be easily compensated by the latent physiological hæmogenic margin, but this is not the case. The pathological lesions are those connected with the destruction of enormous numbers of red cells; not only is each infected cell destroyed, but so also are others not so parasitized. Following Brown, it is justifiable to think that malarial pigment can act as a hæmolysin and, by being taken up by endothelial cells, can bring about their degeneration with associated capillary hæmorrhage.

Modern research has shown that it is the youngest erythrocytes which are the first to be attacked by malaria parasites, and Malamos has expressed the view of Jacobs that a large proportion of malaria parasites are contained in *reticulocytes*.

Often, after a single paroxysm of some pernicious malarial fever, as many as half a million or even one million corpuscles per c.mm. drop out of the normal five millions; and this reduction may go on, as paroxysm follows paroxysm, until the corpuscular richness has fallen to one million, or even less. Malarial oligocythæmia is accompanied by changes in the red cells themselves, such as poikilocytosis, anisocytosis, basophilic stippling, and other signs of degeneration of the red cells (*see* Appendix, p. 1027).

In addition to the destruction of the red cells, there is a marked hæmoglobin diminution of the surviving corpuscles to 50, 20, or even 10 per cent. Consequent upon this there is a diminution of the total hæmoglobin content to an even greater degree.

On the whole, in malaria, as in most anæmic conditions, the corpuscles are larger than normal—particularly those attacked by the parasite, especially the benign tertian. Occasionally we come across genuine megalocytes and, not infrequently, certain very minute dark-coloured, spherical corpuscles, which may be nucleated and of embryonic type. Erythrocytes with basophilic stippling are not uncommon, and until recently most pathologists regarded these granules as evidence of degeneration of the erythrocytes.

The blood-sugar is decreased during the course of malaria fever; this may be a matter of the glucose-content of the blood which is known to be essential for the well-being of the malaria parasite.

In all malarial conditions of considerable standing there is a marked diminution in the volume of the blood; we do not, therefore, at the post-mortem examination find that congestion of the organs which is so marked a feature of most specific fevers.

Leucocytes in malaria. The work of many observers tends to show that the leucocytes are increased during the actual malarial paroxysm, but within a few hours of the onset of the attack the total leucocyte count has fallen to 3,000–5,000 per c.mm., and the ratio of white corpuscles to red changes from the normal 1 : 500 to perhaps 1 : 900. There may, however, be a persisting increase of the leucocytes, especially in subtertian infections of the pernicious type associated with intestinal symptoms, but in the chronic stage the usual diminution in the number of leucocytes is not so pronounced and does not last so long as in kala-azar. D. Thomson has shown that the percentage of large mononuclear leucocytes estimated hourly during an attack of malaria gives a curve which is exactly the reverse of the temperature chart; during the rigor and at the height of the fever the percentage is at its lowest; during the afebrile period it rises again. The increase in the large mononuclear cells may persist for weeks after the patient has seemingly been cured by quinine. Stephens and Christophers have stated that a mononucleosis of 15 per cent. (in the absence of kala-azar) is diagnostic of malaria, and the count is not usually above 20 per cent. A history of fever with a relative leucopenia and an increase of the large hyaline mononuclear cells up to 15 per cent. is, therefore, strong confirmatory evidence of malaria; but a leucocytosis *per se* does not necessarily exclude malaria.

Phagocytosis. The hæmozoin, the detritus of the parasites and red blood-corpuscles, is taken up by the polymorphonuclear leucocytes and large hyaline macrophage cells. A considerable destruction of red blood-corpuscles, both normal and containing parasites, takes place in the spleen, and this process of blood destruction is considered to be one of the principal causes of malarial anæmia. The large number of pigmented macrophage cells in the splenic sinuses is a striking feature of the pathology of subtertian malaria, and the finding of pigment-containing leucocytes in the peripheral blood is proof that the patient is infected. The observer must convince himself that it is true hæmozoin and not dust or dirt on the film, and pigment-bearing leucocytes can best be demonstrated by the thick-drop method. As a rule, when it is present within a large mononuclear cell, there is a good deal of it and it is either yellowish-brown or brown-black.

The estimation of the serum-bilirubin, van den Bergh's reaction, shows a gradual rise during the course of a malarial paroxysm.

Malarial pigmentation may be found in blood from any of the organs previously mentioned, within the endothelial cells of the arterioles and capillaries, as minute grains or actual blocks; it may be aggregated so as to form veritable thrombi and occlude vessels. The spleen and bone-marrow are further distinguished from the other organs mentioned by the position in which the hæmozoin occurs in them. In all organs the pigment is found in the blood-vessels, but only in these two is it found in the cells of the parenchyma as well, and outside and away from the blood-vessels. In the liver it is found in the interstitial or Küpffer cells.

Nature and source of malarial pigment.—The pigment is identical

with that formed within the malaria parasites, and is insoluble even in strong acids; it is altered by potash and is entirely and rapidly dissolved by ammonium sulphide. It is an iron-containing derivative of hæmoglobin which is primarily split up into globin and a pigment—hæmatin, and it is from the latter that hæmozoin is derived. So far as the circulation is concerned, such a pigment is found in no other disease, though as an extravascular pathological product a similar one is found in bilharziasis and certain melanotic tumours; but only in the cells, never in the blood-vessels.

Of all the vessels of the body, the splenic vein is that in which malarial pigment is most abundant. Whereas in other vessels it is found to be included in ordinary leucocytes, in this vessel it is included in large white cells, probably identical with splenic pulp cells. The reason for this is that the spleen is not only the physiological destination of the hæmozoin-laden leucocytes, but is also a favourite nursery of the parasite.

Besides the pathognomonic hæmozoin, there is usually found in the organs a considerable amount of a yellow or brown pigment, *hæmosiderin*. This pigment is found not only in the capillaries, but also in the parenchyma cells of the liver, spleen, pancreas, and kidney, as well as in the bone-marrow and the connective tissues. It is by no means characteristic of malaria, but occurs in all diseases in which there is an extensive breaking up of red blood-corpuscles, as in paroxysmal hæmoglobinuria, in pernicious anæmia, in organic poisonings, etc. Contrary to what has been said about hæmozoin, it is equally insoluble in acids, alkalis, and alcohol.

Apparently, under the name of hæmosiderin two pigments were formerly included, one containing iron, the other not; the latter is known as *hæmofuscin*, though some authorities consider that there is originally one pigment which, after deposition, breaks up into free iron and the iron-free hæmofuscin. The ferruginous granules are more abundant after an active hæmolysis, and can be demonstrated by the potassium ferrocyanide method, in which they show up blue; the hæmozoin (in which the iron is firmly combined) shows up black, while the hæmofuscin remains yellow. In a more protracted hæmolysis, as in chronic malarial cachexia, the yellow pigment alone is found.

Polycholia.—Up to a certain degree of pathological hæmoglobinæmia the liver can deal with the free hæmoglobin; and so it comes about that when this substance is free in the blood, the secretion and flow of bile become correspondingly increased. If this flow of bile be excessive it gives rise to what are called "bilious symptoms"—bilious vomiting, bilious diarrhœa—symptoms which are common in malarial disease, particularly in the variety known as "bilious remittent." Thus, polycholia is a constant and often urgent feature in most fevers, and is good evidence that in malarial infections there is a surcharge of the blood with free hæmoglobin. It is not improbable, although this point is disputed, that the yellowness of the skin and scleræ observed in these fevers is due to tinting of the tissues by the

liberated hæmoglobin, and not, as is popularly believed, to biliousness or cholæmia from bile absorption.

Enlargement of the liver.—In all four types of malaria, but especially in subtertian, enlargement of the liver is apt to occur. In life it is usually accompanied by tenderness of the organ and slight changes. The pathological appearances are due to pigmentation and great congestion; the capillaries themselves may be distended with macrophage cells, endothelial cells, and malarial pigment. The liver cells are usually atrophied and contain much hæmofuscin, while the hæmozoin is found in the interstitial or Küpffer cells. In subtertian malaria there may also be extensive fatty degeneration of the liver cells.

The heart.—In rapidly fatal cases of subtertian malaria Dudgeon and Clarke have found a diffuse fatty degeneration of the heart similar to that occurring in acute diphtheritic poisoning. The recognition of these changes in the heart goes far to explain the dramatically sudden deaths which may occur in subtertian infections.

The suprarenal glands.—In subtertian infections a constant lesion has been noticed in these glands, especially in the reduction of the lipoids of the cortex. It has been thought that these changes explain a syndrome occasionally met with in subtertian fever, characterized by great muscular weakness and low blood-pressure.

Pathology of Blackwater Fever

The microscopic pathology of blackwater fever resembles very closely the pathology of subtertian malaria, already described.

The *gall-bladder* is filled with dark-green viscid bile. The spleen contains a large amount of hæmozoin, together with evidence of phagocytosis of the red blood-corpuscles by the leucocytes and endothelial cells (hæmatophagy).

The *kidneys* are enlarged and congested, and of a peculiar sandalwood or greyish-violet-brown colour, the tubules being blocked with hæmoglobin infarcts, and the cells of the collecting tubules laden with hæmofuscin, while in the capillaries a considerable amount of hæmozoin is found. The blockage of the kidney tubules is attributable, apparently, to two causes: the hyaline or blood-casts, as they are called, are due to the coagulation of highly albuminous hæmoglobin-containing serum, while the cellular are formed by dislodged and degenerate epithelial cells of the urinary tubules which, when impregnated with hæmoglobin, collect in the lumen of the tubules. In more chronic cases of the disease the appearances of the kidney are different. Should the patient then die of uræmia, the macroscopic and microscopic appearances of the kidney are those of a chronic parenchymatous degeneration. The *bone-marrow* is brown and of a fluid consistency.

In the early stages of blackwater fever the *blood* shows a great reduction in the number of red blood-corpuscles, but very little other change; the degree of reduction depends upon the extent of the hæmolysis. If it is very extensive, the red blood-corpuscles may fall to 1 million per c.mm. within 24 hours, but in fulminating cases counts of 500,000 have been recorded. At this stage free "shadow" corpuscles can be seen in fresh blood preparations, and it is said that effete red cells may occasionally be found enclosed in the phagocytes. During the stage of recovery the most striking microscopical changes seen are the intense polychromasia and polychromatophilic stippling of the red blood-corpuscles. According to the recent teaching, both these changes are held to be indicative of blood regeneration, and, as evidence

of this, nucleated red blood-corpuscles may make their appearance; at the same time, as a rule, a definite increase of the mononuclear cells above 12 per cent. can be substantiated; but, save in the absence of malaria parasites, there is no striking feature in which the blood picture differs from that of a pernicious case of subtertian malaria.

Clinical Phenomena of Malaria Fever

Symptomatology.—Formerly the malaria fevers were divided into intermittent or remittent forms (*see* p. 74), but it has since been found that intermittency or remittency is more or less an accident, for any of the three parasites already described may cause what was formerly known as remittent fever. Two generations of tertian parasites maturing on two successive days will produce a quotidian fever; but two generations of quartan parasites maturing on successive days will give rise to fever on two successive days followed by one day of freedom from fever—what is known as *Quartana duplex;* whereas three generations maturing on three successive days will produce a quotidian fever—*Quartana triplex.*

Each attack of malaria fever consists of a stage of coldness or rigor (ague), a stage of heat, and a stage of sweating; these are followed by a period of apyrexia known as the interval. The duration and intensity of these constituent stages vary very considerably.

The incubation period.—This is usually stated as being about ten days; but James finds that, under experimental conditions, the mean period, by mosquito-bite, is 14·1 days; but when caused by blood inoculation 11·2 days. There is a tendency for the incubation period to become shorter, especially in subtertian malaria, and for the attacks to be more severe as the number of bites is increased. In some 3.5 per cent. the incubation period may be as short as eight days; in addition there are *latent* cases in which the incubation period is between 30 and 40 weeks.

Premonitory stage.—Before rigor sets in, and sometimes for several days before the actual disease declares itself, there may or there may not be a premonitory stage marked by lassitude, a desire to stretch the limbs and to yawn, aching of the bones, headache, anorexia, perhaps vomiting; perhaps a feeling as of cold water trickling down the back. If the thermometer be used, it will be found that body-temperature has begun to rise, it may be some two or three hours before the onset of the other and more striking symptoms which ensue; or it may be that the threatened attack will subside spontaneously without culminating in the more pronounced phenomena of a fully-developed ague.

Cold stage.—When rigor sets in, the feeling of cold spreads all over the body, becoming so intense that the teeth chatter and the patient shivers and shakes from head to foot. He seeks to cover himself with all the wraps he can lay hands on. Vomiting may

become distressing. The features are pinched, the fingers are shrivelled, the skin is blue and cold-looking, and may exhibit the condition known as "goose-skin" (cutis anserina). But the feeling of cold is entirely subjective; if the temperature be taken it is found to be already several degrees above normal and to be rapidly mounting. In young children it is not at all unusual to have a convulsive seizure at this stage—a fact that has to be borne in mind, as it is very apt to suggest ideas of epilepsy.

Hot stage.—After a time the shivering gradually abates, giving place to, or alternating with, waves of warmth and, before long, to persisting feelings of intense heat and febrile distress. The wraps, which before were so eagerly hugged, are now tossed off; the face becomes flushed; the pulse is rapid, full, and bounding; headache may be intense; vomiting frequent; respiration hurried; the skin dry and burning, the thermometer mounting to 104°, 105°, 106° F., or even higher.

Sweating stage.—After one or more hours of acute distress the patient breaks out into a profuse perspiration, the sweat literally running off him and saturating his clothes and bedding. With the appearance of diaphoresis the fever rapidly declines; headache, vomiting, thirst, and febrile distress giving place to a feeling of relief and tranquillity. By the time the sweating has ceased the patient may feel quite well: a little languid, perhaps, but able to go about his usual occupation. The bodily temperature is now often subnormal, and may remain so until the approach of the next fit, one, two, or three days later. Herpes of the lips is a common manifestation of malaria, especially in benign tertian infections; a similar affection of the ears has also been noted, while true herpes zoster of the body may also occur.

Duration of the fit.—The duration of an ague fit and of its constituent stages is very variable. On an average it may be put at six to ten hours, the cold stage occupying about an hour, the hot stage from three to four hours, the sweating stage from two to four hours.

The urine and fæces in ague.—During the cold stage the urine is often limpid and abundant, and is passed frequently; but during the hot, sweating stages it is scanty, loaded, sometimes albuminous. The amount of urea is increased, particularly during the cold stage, and so are the chlorides and sulphates. The phosphates, on the contrary, diminished during the rigor and hot stages, are increased during defervescence. The augmentation in the excretion of urea commences several hours before the subjective symptoms of the attack begin, attains its maximum towards the end of rigor, and decreases during the hot and sweating stages, although still continuing above the normal standard. The excretion of carbonic acid follows a corresponding course. The urine usually contains urobilin, which is increased during the attack, but declines directly the temperature

falls. The corresponding pigment in the faeces (hydrobilirubin) is increased to twenty times the normal amount as long as there is fever and parasites are present in the blood.

The spleen during the fit.—The spleen usually becomes enlarged to a greater or less extent during the rigor, but is not always palpable. At first the swelling disappears in the interval, but it tends to become more or less of a chronic feature if the attacks recur frequently, more especially if they are associated with pronounced cachexia. Spontaneous rupture may occur, though rarely, in acute stages of inoculated malaria, after injury to the abdomen, necessitating splenectomy. The operation, however, does not extirpate the malarial infection, as has sometimes been stated. Hennessy has noted that the symptoms of rupture of the spleen may simulate those of rupture of the bladder owing to the presence of pain in the hypogastrium and the irritation of the latter. Failure to palpate the spleen should not deter the diagnostician from making a routine blood examination for malaria parasites since these may often be found in the absence of any ascertainable splenomegaly.

Period of the day at which ague commences.—A large proportion of agues "come off" between midnight and noon, or in the early afternoon. This is a fact to remember in diagnosis; especially when we have to face the possibility of recurrent pyrexial attacks being caused by such conditions as liver abscess, tuberculosis, and septic states– conditions, be it remarked, in which febrile recurrence takes place almost invariably during the afternoon or evening.

Atypical agues.—There are some cases of subtertian malaria, especially of African origin, which are liable to assume suddenly a pernicious character. In other cases, notwithstanding a comparatively slight rise of temperature, supraorbital neuralgia, headache, prostration, or vomiting may be extremely distressing. There is an infinite variety in this respect.

Terms employed.—Acute malarial attacks which recur daily are called *quotidian ague;* if they occur once in 48 hours, they are called *tertian ague* (Chart 1); if once in 72 hours, *quartan ague* (Chart 2). As a rule, the attacks tend to occur about the same time every day. When the fit is prolonged and periodicity is marked by only a slight fall of temperature, a slight sweating, a slight feeling of chilliness, the fever is said to *remit*—to be *remittent.* Sometimes there is no remission; such a fever is said to be *continued.* When a fever oscillates above and below the normal line from day to day, it is said to be *intermittent.* James distinguishes between a *recrudescence* and a *relapse;* by the former term is meant a return of clinical symptoms following a short time after the primary attack; a relapse, on the other hand, occurs after a considerable interval—it may be months—during which there is no fever and the patient enjoys good health. The causation of the two is probably different and relapses are more liable to come on during cold weather.

All sorts of blending of subtertian with tertian, and occasionally of either or both with quartan, may occur; these are cases of *mixed* infection.

Relation of the phenomena of the fever to the developmental

stages of the parasite.—During the rigor the segmenting parasites are breaking up and are liberating the merozoites, which escape into the peripheral blood. At the end of the rigor and during the hot and sweating stages, the young parasites of the new generation—small and intracorpuscular bodies or schizonts—and pigmented leucocytes containing the hæmozoin liberated by the breaking-up of the fully-formed schizont, can be demonstrated.

During the apyrexial interval, the intracorpuscular parasites are growing in size, becoming pigmented, and preparing for maturation. From the fact that parasites are present in the blood during apyrexia, often in great numbers, it is evident that it is not the mere presence of the parasite in the blood-corpuscle which causes the fever, but probably the pyrogenic agent is in the nature of an anaphylactic or " hæmoclasic " shock. Abrami and Senevet have applied this term to a condition resulting from the inoculation of foreign proteins into the blood-stream ; the phenomena consisting chiefly of lowered arterial tension, leucopenia, a diminution in the number of red cells and changes in the coagulability of the blood. Most probably the showers of liberated merozoites or the products of the destroyed red blood-corpuscles act as the foreign protein injected into the blood-stream.

Course of benign tertian and quartan fevers.—Benign tertian fever usually lasts ten hours or less and corresponds in the main to the description of a typical malarial attack already given. In some cases the rise of the fever is rapid and high, and the temperature may reach 105° or 106° F. within an hour or so : on the other hand, cases are met with in which none of the clinical phenomena of malaria fever are present, and the temperature does not rise above 99–100° F. The fever in quartan infection is generally smart while it lasts, and well defined as regards the various stages, but it does not tend so markedly as in other malaria infections to the rapid development of cachexia. It has often been noted that, although individual attacks of this infection are amenable to quinine, the disease itself appears to be of a more persistent nature than tertian or subtertian malaria. Attacks, therefore, are liable to recur during several years. The parasites, too, are more resistant to quinine in one sense, in so far as they persist in the blood-stream for a week or more whilst the patient is taking this drug.

Course of ovale tertian malaria.—This type of fever closely resembles the benign tertian in its periodicity ; but, generally speaking, the attacks are sudden, short and mild, and not accompanied by any grave degree of anæmia or constitutional disturbances. The rigors in this type, in contradistinction to other forms of malaria, are more apt to take place during the course of the evening. Rheumatic-like pains in various parts of the body, especially the lumbar region, are characteristic, and sometimes pain referred to the appendix may suggest a diagnosis of appendicitis. Very rarely, more severe types with splenomegaly and anæmia are met with, though in these cases a mixed infection with subtertian malaria may be suspected. There is usually no excess of urobilin in the urine which is usually found in other species of malaria infection associated with intense blood destruction.

Quartan malaria nephrosis.[1]—Nephrosis is common in those countries in which the quartan parasite predominates. This question has been studied by Watson (1904), and Clarke (1912), in Malaya, by Goldie in Palestine, by Daniels (1897), by Giglioli in British Guiana, and by Surbek in Sumatra. The Editor, with Maybury (1927), reported two cases of acute nephrosis in which the presence of the quartan parasites ran parallel to the amount of albumin in the urine. Giglioli, in his complete study, finds that acute *nephritis* is not usually associated with this infection except in the chronic form, and considers that a small proportion of cases are caused by *P. falciparum* as well. Both sexes are liable to this complication; in childhood the sex distribution is equal, but amongst adults malarial nephritis is commoner in males than in females. He regards albuminuria occurring in a febrile attack as indicating the commencement of parenchymatous nephritis. The pathology consists of an inflamed kidney which afterwards becomes of the large white variety and eventually degenerates into chronic interstitial nephritis. Goldie, on the other hand, finds *that the pathological picture* is one of "nephrosis" and is due to the production of malarial toxins continued over a long period. He considers that this may occur in all types of infection, especially the subtertian, but he thinks that the liability in quartan cases is due to insufficient treatment on account of their milder character, and that thus they are more liable to relapse into the chronic stage.

As a general rule, the duration of one benign tertian infection before the parasites die out from the peripheral blood is nine months to a year after leaving the endemic area, but exceptions to this rule often occur; clinical relapses, with the presence of the parasite in the blood, have been recorded as long as three and even four years after the date of the original infection. Quartan is the most resistant and persistent infection.

Characters of Subtertian or Malignant Fevers

From a clinical point of view as regards diagnosis and treatment, this is the most important form of malaria. As a rule, the fever produced is very irregular in its course. *The rigor stage is relatively less marked;* the pyrexial stage is more prolonged, and is often characterized by a tendency to adynamic conditions, together with vomiting, intestinal catarrh, pains in the limbs, anorexia, severe headache, supraorbital neuralgia, and depression. After apparent recovery from the fever, there is a great proneness to relapse at more or less definite intervals of from eight to fourteen days, but an immunity soon appears to develop. Experience gained during the Great War has tended to show that benign tertian infections are, as a rule, far more persistent than are the subtertian. Subtertian fevers are accompanied by rapid destruction of corpuscles, and are usually followed by

[1] According to the modern classification of Müller, the term "nephrosis" should be retained for the toxic "nephritis" of malaria and allied conditions.

marked cachexia. At any time in their course, but more especially during primary infections, symptoms of the gravest character may declare themselves.

As a general rule, the associated symptoms are in many respects

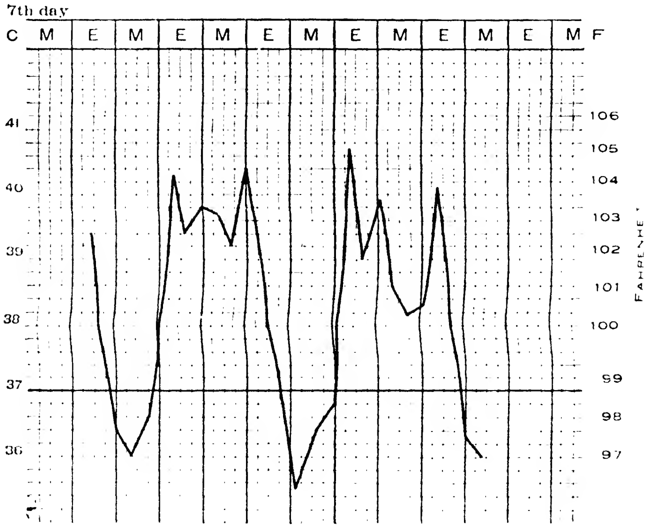


Chart 4.—Subtertian fever (*P. falciparum*).

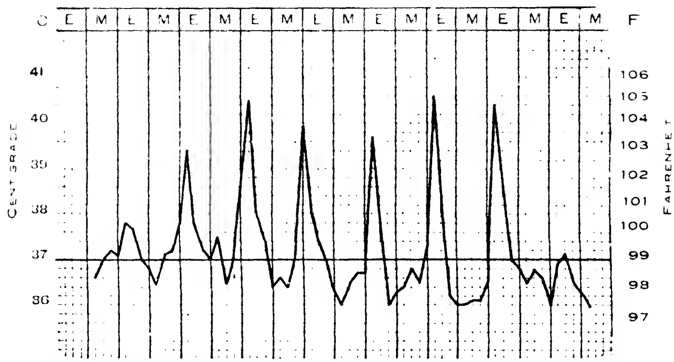


Chart 5.—Quotidian fever (two generations of *P. falciparum*).

very different from those caused by the tertian parasite. In the first place, although rigor is not so marked, the hot stage lasts longer—often exceeding twenty-four hours: in fact, the tendency for the successive paroxysms to overlap, to become subintrant, is very marked. Moreover, when the intermissions are distinct the crisis is generally

unlike that of ordinary tertian. There is frequently what is called a *double crisis ;* that is to say, when the fever has attained its apparent fastigium there is a drop of one or more degrees of temperature—the "false crisis"—to be followed by a fresh rise, which is then succeeded by the "true crisis." This peculiar phenomenon has been attributed to the presence of two swarms of parasites, one of which matures somewhat later than the other; it is only proved to occur regularly in one other tropical fever, namely, kala-azar. (Chart 4.)

A double infection with the subtertian parasite may produce a quotidian fever (Chart 5), a typhoid-like depression generally being a marked feature.

This form of fever is justly regarded as being dangerous to life, yet in certain instances the parasite may exist, even in considerable numbers, in the blood-stream for months on end without seriously interfering with health; it may produce no ascertainable rise of temperature, or the patient may eventually seek medical aid suffering from œdema of the legs, dyspepsia, or some other bizarre or trifling complaint apparently quite unconnected with malaria. Cases of this nature are frequently seen in men returning from the West Coast of Africa, in whom the first symptoms of ill-health may appear after several months' residence in England. As the infection is capable of lying dormant for a long period, one should examine microscopically the blood of every patient coming from a malarious country, whatever the nature of his complaint, since often this parasite in the ring or crescent stage, is found in the blood of apparently perfectly healthy individuals, usually without splenic enlargement or other signs of malaria, on their return to Europe from West Africa. The one outstanding clinical sign which is of value in these latent cases is the deep sherry colour of the urine, due to the presence of urobilin (*see* Appendix, p. 1027). Though subtertian malaria may produce the most virulent infections and may be in many instances a danger to life itself, yet they are much more amenable to quinine and atebrin than are the benign tertian. The life of the parasite in the human body is much shorter, and it is extremely rare for relapses of subtertian malaria to be noted nine months to one year after quitting the endemic area of the disease.

The clinical guises which subtertian malaria may assume are most protean in character. It may markedly simulate many other tropical fevers, and even surgical conditions. The following are the main clinical types of this fever that are recognized:

Bilious remittent.—One type of malarial fever—bilious remittent—has long been recognized on account of the bilious vomiting, gastric distress, sometimes bilious diarrhœa, sometimes constipation, which accompany the recurring exacerbations. It is further distinguished by the pronounced icteric or, rather, reddish-yellow or saffron tint of skin and scleræ a tint derived, probably, not from absorption of bile as in obstructive jaundice, but from modified

hæmoglobin (serum bilirubin) free in the blood or deposited in the skin and sclerotics. These bilious remittents are very common in the more highly malarious districts of Africa, America, the West Indies, India, and, in fact, in all malarious tropical countries. They are not usually dangerous in themselves, but they are apt to result in profound anæmia, and are often but the prelude to chronic malarial saturation, bad health and invaliding.

A modification of the bilious remittent—the "typhoid remittent"—is very much more grave, as affecting life, than the simple bilious remittent. In the typhoid remittent, typhoid symptoms—such as low delirium, prostration, dry tongue, swelling of spleen and liver, subsultus tendinum—are superadded to the usual symptoms. Though recovery is the rule, a considerable proportion of such attacks prove fatal.

Some writers class by themselves a set of cases they call "adynamic remittent"—cases which are characterized by restlessness, nervous depression, intense muscular and cardiac debility, profound and rapid blood deterioration, icterus, liability to syncope, occasionally a transient hæmoglobinuria (as was observed in some of the Salonika cases), liability to hæmorrhages, and a marked tendency to local gangrene.

Tuberculosis, syphilis, renal disease, or alcoholism will often be found as factors in determining the adynamic remittent and typhoid remittent types of fever.

Pernicious attacks.—Many writers have drawn attention to what are called pernicious attacks or pernicious symptoms—the French neatly designate them *accès pernicieux*—a series of phenomena of the possibility of which, not only in the course of remittents but in the course of what is seemingly an ordinary paroxysm of intermittent fever, the practitioner in tropical climates should never lose sight. These *accès pernicieux* may supervene in apparently mild cases and carry off the patient with horrifying suddenness—as suddenly as an attack of malignant cholera. The wary practitioner is always on the look-out for them, and is always prepared with measures to meet them properly when they threaten. Pernicious attacks are liable to develop in drug addicts (*see* p. 56).

Pernicious attacks are roughly classified into cerebral and algid. The cerebral are divisible into hyperpyrexial, comatose, convulsive, paretic, and so forth; the algid into syncopal, choleriform, hæmorrhagic, etc.

Cerebral forms. *Hyperpyrexia.*—There can be little doubt that many of the cases of sudden death from hyperpyrexia and coma usually credited to what has been called "ardent fever" or "heat-apoplexy," are really malarial in nature. If careful inquiry be made into the antecedents of many of these cases, a history of mild intermittent fever will often be elicited; or it will be found that the patient had been living in some highly malarious locality.

In the course of what seemed to be an ordinary malarial attack the body-temperature, instead of stopping at 104° or 105° F., may continue to rise and, passing 107°, rapidly mount to 110° or even

to 112°. The patient, after a brief state of maniacal or, perhaps muttering delirium, becomes rapidly unconscious, then comatose, and dies within a few hours, or perhaps within an hour, of the onset of the pernicious symptoms.

Coma.—Sometimes the patient, without hyperpyrexia, the thermometer perhaps not rising above, or even up to, 104°, may lapse into coma. The coma may pass away with a crisis of sweating; on the other hand, an asthenic condition may set in and death from collapse supervene. In these cases there is a marked increase of pressure in the cerebro-spinal fluid, and the Editor has found intracellular melanin pigment to be a striking and diagnostic feature. Appelbaum and Gelfand have recorded an increase in the large mononuclear cells and a definite increase in the albumin and globulin in this fluid.

Epileptiform attacks.—There has been some divergence of opinion regarding the origin of epilepsy following malaria. Mohr thinks that the symptoms are sometimes those of meningitis, and numerous lymphoid cells are found in the cerebro-spinal fluid. From the resulting destruction of brain substance in cerebral malaria manifold symptoms of central nervous disturbance may arise, including epileptiform attacks which may follow malaria at widely different intervals.

Malarial amblyopia.—In rare instances a comatose pernicious attack eventuates in blindness. The amblyopia is usually transient, lasting for an hour or two only. On the other hand, it may be persistent: in which case optic neuritis, peripapillary œdema, extravasation of leucocytes, plugging of retinal and choroidal vessels by parasites or pigmented leucocytes, and consequent multiple hæmorrhages, may be found in the fundus. The disc itself is rosy or cherry-pink in colour which, in itself, is considered diagnostic. If the hæmorrhages are minute they are discoverable by the microscope only; on the other hand, large retinal hæmorrhages do occasionally occur. There may be blurring of the edges of the discs (Appelbaum and Gelfand). (In the modern literature of malaria there are very scant references to the fundus changes. Raynaud in 1892, in a monograph, described the fundus changes in great detail, and de Mussy in 1872 first described retinal hæmorrhages.) These fundus changes differ from those in quinine amblyopia. In the latter, depending on retinal anæmia from toxic spasm of the arterioles, the amblyopia is more persistent; the discs are white and the vessels shrunken; there are no inflammatory symptoms; and central vision is the first to recover.

Other cerebral forms.—Besides these hyperpyretic and comatose conditions, other forms of cerebral attack may occur in the course of malarial fevers. Thus, there may be *sudden delirium* ending in coma and, perhaps, death; conditions simulating *cerebro-spinal meningitis*; *delusional insanity*; *dementia*; *acute alcoholism*; various forms of *apoplectic*-like conditions and of *paralysis*, complicated, it may be, with *aphasia*. Seizures of this description, if not fatal, may eventuate in *permanent psychical disturbances*, with a tendency to *suicide*. Temporary debility, or even complete *loss of memory*, may succeed severe malarial infection.

Embolism of cerebral capillaries.—These cerebral attacks are now explained and, it appears, correctly explained, by the supposition, founded on actual post-mortem observation, that they depend on embolism by malaria parasites of the capillaries of the various nerve-centres involved: in hyperpyrexia, the thermic centres; in aphasia, Broca's convolution. Monoplegia or hemiplegia, and so on, may result from implication of special brain areas. By microscopical examination of properly prepared sections of the brain in fatal cases, such a plugging of the vessels can, as a rule, be readily observed. In association with this condition focal degenerations of the brain substance also have been noted (Fig. 7).

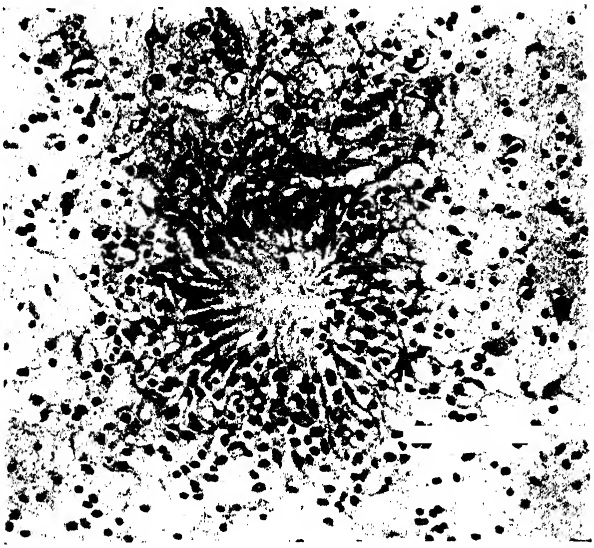


Fig. 7.—Malarial granuloma. Brain section showing plugging of capillaries of cortex. (*Archiv für Schiffs- und Tropenhygiene.*)

Algid forms.—The algid forms of pernicious attack, as indicated by the name, are characterized by collapse, extreme coldness of the surface of the body, and a tendency to fatal syncope. These symptoms usually coexist with elevated axillary and rectal temperature.

Gastric form.—This may be associated with, and in a measure be dependent on, acute catarrhal dyspeptic trouble. It is accompanied by severe epigastric distress, tender retracted abdomen, and incessant vomiting. The vomited matter may contain blood.

Choleraic form.—Malarial attacks are sometimes accompanied by choleraic symptoms. The stools suddenly become loose, profuse,

and numerous, but generally not so profuse or colourless as the rice-water discharge which pours from the patient in true cholera; they retain a certain amount of biliary colouring, and may be mucoid, or even bloody. As in cholera, the serous drain may lead to cramps in the limbs, loss of voice, pinched features, "washerwoman's fingers," almost entire suppression of urine, and perhaps to fatal collapse. The high axillary temperature, if present; a history, maybe, of recent ague fits; the subsequent rapid cessation of choleraic symptoms on the appearance of the hot and sweating stages; the colour of the stools, and other collateral circumstances, usually suffice for diagnosis, particularly if they are supplemented by a microscopical examination of the blood. Although not usual, recurrence of the choleraic symptoms may take place at the next fever period. This dangerous type of malarial fever was noted in Salonika and Palestine during the Great War, and is said to be prevalent in the Punjab. Without the microscope its true nature may be hard to recognize.

Dysenteric forms.—Another form of pernicious attack is characterized by the sudden appearance of dysenteric symptoms, by severe and recurring hæmatemesis, or by hæmorrhage from the bowel or elsewhere. The possibility of a suddenly developed hæmorrhage of this nature from the bowel being of malarial origin must therefore be kept in view; particularly if, in what at first sight appears to be ordinary dysentery, the axillary temperature is found to be abnormally high.

Occasionally, in the Editor's experience, it has been possible to demonstrate intracorpuscular subtertian malaria parasites in stained preparations made from the stool. M. Arafa has described the sigmoidoscopic appearances in which diffuse hyperæmia and swelling of the mucosa are observed as in bacillary dysentery, and in preparations made from the ulcerated surface he was able to confirm the diagnosis by finding subtertian crescents in the exudate.

Hæmorrhagic forms.—As in purpura, so in these pernicious attacks, hæmorrhages may occur in almost any organ. When this takes place in the brain or spinal cord it may produce a monoplegia, a diplegia, or even a complete hemiplegia. The effect of these paralyses may be transient or permanent.

Purpuric hæmorrhages into the skin may be generally distributed over the body. They are of rare occurrence, and are commonly associated with better-known phenomena of malaria fever.

Œdema.—General anasarca with chronic subtertian malaria has been noted in debilitated subjects as, for instance, in war refugees in Greece and in the great Ceylon epidemic of 1934. Wickramasuriya noted œdema in 40 per cent. of 357 cases specially investigated in pregnant native women.

Syncopal form.—In the preceding types of pernicious algid malarial attack the dangerous symptoms mostly show themselves in the rigor stage of the fever. There is yet another form in which the danger appears to depend on an exaggeration of the symptom usually hailed

as bringing relief and, for the time, freedom from danger. Thus the sweating of the stage of defervescence may be excessive and cause collapse which, if the patient rise up suddenly or make an undue effort, may lead to fatal syncope. Weak and cachectic patients, therefore, should be warned of this possibility. Death from suddenly developed cardiac failure is common in the pernicious forms of subtertian malaria, and is due to the severe toxic fatty degeneration of the myocardium (Dudgeon and Clarke).

Acute hæmolytic anæmia.—There is a rapidly developing and progressive anæmia in the fourth or fifth week of a primary subtertian attack, comparable only to what is seen in the most advanced stages of pernicious anæmia. These cases are characterized by great pallor of mucous membranes and conjunctivæ, cardiac distress and dyspnœa, hæmic murmurs, and retinal hæmorrhages; the blood-picture by a blood-count of under 1,000,000, extreme leucopenia, a reduction of hæmoglobin to 10 per cent. or under, and the appearance of macrocytes and megaloblasts in the blood. The pathology of these conditions indicates the hæmolytic nature of the malaria toxin and its action upon the bone-marrow, which shows megaloblastic response. In consequence of the bone-marrow changes and the inhibition of leucocyte production, sufferers from subtertian malaria are more susceptible to secondary infections of all kinds.

Rarer clinical forms of subtertian malaria.—Pulmonary forms have been described, with congestion of the pulmonary vessels and bronchitic symptoms. Rare cases with rapidly developing anasarca and ascites were observed in Macedonia and in Palestine during the Great War; and, lastly, œdematous forms with nephritic signs, such as the presence of blood-cells in the urine, have been noted. Gangrene of the toes, and disturbances in the vaso-motor mechanism, as in Raynaud's disease, have been met with in subtertian malaria.

A practical experience of these suddenly developed pernicious fevers of the tropics teaches that we should never make light of any malarial attack, particularly if it be of a mild irregular character and imperfectly controlled by quinine, and if small parasites, or the crescent form, be present; the practitioner should be on the alert for any danger signal—mental aberration, restlessness, tremor, peculiarity in behaviour, alteration in knee reflexes, and other indications of grave implication of the nervous system. It further teaches that the subjects of such fevers should be particularly careful to guard against chills, fatigue, insufficient or unwholesome food, etc.

Malaria in pregnancy.—The development of pernicious symptoms is liable to occur in pregnant women infected with *Plasmodium falciparum*. Cerebral manifestations in late pregnancy arising unexpectedly, without any previous malarial history, may give rise to serious diagnostic difficulties. The majority are diagnosed as eclampsia. The epileptiform in pregnancy is better termed "the eclamptic." A lucid interval is very liable to ensue in consequence of intravenous

quinine therapy and is liable to lead the inexperienced physician astray.

"Latent" malaria is very apt to persist in pregnancy only to be woken up during parturition, or lactation. Wickramasuriya, who has adequately surveyed this subject, finds that malaria can modify the course of pregnancy by spontaneous interruption before term; indeed, malaria *per se* is a far more potent oxytocic than any drug, especially in the ill-nourished who are also infected with ancylostomiasis. Intra-uterine death of the fœtus is fairly frequent, whilst clinical and pathological evidence points to malaria as a powerful predisposing factor in the toxæmias of pregnancy, such as pre-eclampsia, eclampsia, and "nephritic" toxæmia. In subtertian malaria albuminuria and œdema of renal origin make their appearance. Hypertension, that most important criterion of pregnancy toxæmia, is often noted. Greater dangers are to be anticipated when the disease occurs in the later than in the earlier months of pregnancy.

Malaria in small children.—Malaria, especially of the subtertian type, is proportionately a much more severe disease in children than in adults. Benign tertian malaria frequently produces the most alarming symptoms in babies in arms, but it is not necessarily very severe and is easily controlled; it is otherwise in subtertian malaria, which is especially liable to assume the cerebral form in the young, and must always be regarded in a serious light.

Complications.—Subtertian malaria may complicate, or be complicated by, almost any other disease; a common and very fatal terminal event is pneumonia of either the lobar or broncho-pneumonic variety, noticeable in the influenza epidemic of 1918. When associated with enteric, this greatly complicates the clinical picture. The same may be said of the main forms of dysentery. Pulmonary tuberculosis is very liable to supervene in cachectic cases. It should be noted, too, that a malarial relapse may take place after any surgical operation, or after parturition, or shock or strain of any description, in a subject previously infected; and surgeons in the tropics would do well to bear this fact constantly in mind.

A phenomenon occasionally observed in pernicious attacks, especially in those of an algid type, is the flooding of the peripheral blood with vast numbers of parasites, it may be at all stages of development—gametes as well as schizonts. The prognosis in such cases is usually bad. On the other hand rare instances are seen when this occurs in an attack of average severity.

Malarial "orchitis."—Orchitis occurring in the course of a malarial attack may be due to the presence of parasites in the testes. Cases have been reported by Mayer and by Bastillo, and the parasites have been demonstrated in the vessels of that organ, post mortem.

The chief and most dramatic sequel is undoubtedly blackwater fever.

BLACKWATER FEVER

Synonyms.—Malarial Hæmoglobinuria; Hæmoglobinuric Fever.

Definition.—The disease consists in an acute hæmolysis of the red blood-corpuscles, which liberates the hæmoglobin into the blood-stream, and in turn produces hæmoglobinuria. There are certain points of analogy between this complication of malaria and the disease known as *paroxysmal hæmoglobinuria*.

Geographical distribution.—The disease has attained its greatest notoriety, and is undoubtedly most prevalent, in Europeans on the West Coast of Africa, from Senegal to the Quanza, but principally on the Congo and in the deltas of the Niger and Gambia rivers. On the East Coast it is also widely spread, especially along the Zambesi, the lower Shiré, and the shores of Lake Nyasa. It is far from uncommon on the Upper Niger, in British East Africa (including Tanganyika Territory), in Uganda, in North and South Rhodesia, in Abyssinia, in the valley of the Upper Nile and in Algeria. It is also common in some parts of Madagascar.

In America it is found, but not so extensively as formerly, over the Southern States of the Union, chiefly Florida. Georgia, Alabama, Mississippi, Arkansas, and Texas; but it has also been prevalent in North Carolina and Virginia. It is found, too, in Central America; in the Guianas, where it has been studied by Giglioli; on the Upper Amazon; in the plains of Venezuela; and in the West Indies; but it has disappeared from the Canal Zone since the introduction of anti-malaria measures.

In Europe it is restricted to Bulgaria, Macedonia, where it is very common, Albania, Greece. Sicily, and Sardinia. A few cases may have been recorded in Central Italy.

In Asia it is reported from Palestine, especially the Jordan valley, from Tonquin, the Malay Peninsula, Formosa, from India, particularly Bihar, Assam, Darjeeling, the Terai, Dooars, Meerut, and Amritsar, from Burma and Northern Siam, and from the province of Yunnan, China. It occurs in many of the malarious islands—Java, etc.—of the Eastern Archipelago; also in New Guinea and the Solomons.

Blackwater fever occurs not uncommonly in England in individuals of both sexes who have been infected with subtertian malaria in West Africa and other highly malarious countries. In these people it is apt to break out after exposure to cold, overdosage with alcohol or quinine, within a period as long as eight months after their arrival in a temperate climate. Such cases are, as a rule, very acute and the mortality-rate is 50 per cent. or even higher.

Epidemiology.—At times blackwater fever appears to assume an epidemic form. It may not be seen for years in a district, and then numbers of cases may occur within a short time. Very often, as is the case in yellow fever, the magnitude of an "epidemic" may depend on the number of susceptible persons—new arrivals, it may

be other than Europeans—within the endemic region ; as, for instance, Bengali clerks in the Punjab, Egyptians in the Sudan, Chinese imported into British Guiana, negroes in Panama, and Central African natives when taken to the high altitudes of the great African mountains. Thus it broke out among the labourers employed in making the canal through the Isthmus of Corinth, and attacked the Chinese labourers on the Congo Railway. It is recorded that more than 60 per cent. of the European medical casualties in the German East African force under von Lettow were due to blackwater fever.

Blackwater was until recently rare in West African negroes, but it is as frequent in Arabs and Hindus as in Europeans ; amongst the latter fair people appear more susceptible than dark. Reyntjens, and also Chesterman, emphasize that, under normal conditions, the negro child, during its first year of life, escapes blackwater though it frequently dies of malaria. When, however, it is protected against the effects of malaria by quininization, it becomes susceptible to blackwater.

The occurrence of several cases in the same family may not be pure coincidence, but probably is explained by exposure to a common factor. This has given rise to the term " blackwater-fever houses " in certain districts, especially in Rhodesia, but when investigated they are proved to be bungalows with exceptionally bad surroundings, and highly malarious. In British Guiana Giglioli has observed the same features—the tendency for blackwater to occur as a family or house disease, and for it to appear in a given locality at approximately the same period.

Ætiology.—The ætiology of blackwater fever has been the subject of considerable controversy, much of which is now a matter of history. At present it is generally recognized to be the result of repeated attacks of, or continuous infection with, subtertian malaria.

Drug theory.—Those who favour this theory believe that quinine, even in small doses, may produce the manifestation of blackwater fever in patients in whom the malaria infection is latent. But quinine, even in poisonous doses, never produces blackwater fever in healthy people or in persons uninfected with the subtertian parasite, and a special hypothetical idiosyncrasy has therefore to be assumed. Possibly the issue has been confused by the fact that in susceptible, but otherwise normal, individuals the administration of quinine may produce a transient hæmoglobinuria, as in the instances cited by Manson, Gordon Thomson and Macmillan ; whenever it is given, hæmoglobinuria develops within an hour. The fact remains that blackwater fever was known long before the introduction of cinchona bark into Europe ; indeed, it was known to Hippocrates.

Connal, in Nigeria, has recorded 24 cases of severe blackwater in negroes who had never taken quinine and has demonstrated from the death-rates that regular quinine-takers are less liable to a fatal attack than those who have taken this drug in an irregular fashion. His figures are :

Regular takers	19·23 per cent.
Irregular takers	25·00 „
Seldom takers	38·62 „

Mühlens and Knabe have published a case of extraordinarily pronounced quinine susceptibility in a young seaman from West Africa. It was found impossible to accustom him to quinine; less than 1 grain of quinine urethrane produced blackwater. On the other hand, his tolerance to plasmoquine was unusual—a total of 4·75 grm. failed to banish the parasites from his blood.

Blackwater fever may supervene after the administration of plasmoquine, and of atebrin in the Editor's experience, while Foy and Kondi have recorded two cases which commenced on the first and third day after a full course of atebrin and in a third case hæmoglobinuria appeared in a boy of five on the fourth day of atebrin treatment. It seems that any drug of value in the treatment of malaria may predispose to blackwater fever.

Malaria theory.—It has been observed that, although blackwater fever is co-endemic with malaria in several regions, it is not so in all parts of the world. It has its own peculiar distribution, being absent or very rare in many fever-haunted places. It is exceedingly common among the few Europeans who live on the West Coast of Africa, and it is also met with on the East Coast, though to a lesser extent; but it is practically unknown among the many thousands of Englishmen who live in the fever haunts of India and elsewhere, and it is of comparatively frequent occurrence in malaria-infected individuals shortly after their arrival in a temperate climate from the tropics. To Deeks and James in Panama must be given the credit of definitely associating the subtertian malaria parasite with blackwater fever and of successfully demonstrating that measures devised for suppressing malaria are singularly efficient in extirpating blackwater fever.

The production by James of blackwater fever, in paralytic subjects artificially inoculated with certain strains of subtertian malaria, and the analogous effects brought about by massive infection of monkeys (*Macaca*) injected with *Plasmodium knowlesi*, have shed a new light on this subject.

In therapeutic malaria no case of blackwater has ever been observed in association with *P. vivax* infection, but solely with *P. falciparum*.

A condition resembling blackwater fever has been described by Schüffner and Snijders in Sumatra. The patient died twenty hours from the onset, and leptospiræ resembling *L. icterohæmorrhagiæ* were found in all organs, but especially in the liver and spleen and in the kidney, in which situation they occurred within the urinary tubules. Benign tertian parasites were present in the blood as well, while inoculation of blood into guinea-pigs produced a transitory pyrexia, but not the deep icterus of Weil's disease.

Predisposing causes.—Individuals of all ages and both sexes are liable, but from consideration of the facts already put forward it is obvious that it occurs more frequently in European men of mature years who live in the countries where the disease is endemic. At one time race was considered an important factor. In Africa, Europeans, Indians, and Chinese are attacked, while the natives enjoy a relative immunity: this is probably not racial but an active immunity acquired by infection with subtertian malaria during childhood. Negroes who live in places which are free from this disease develop blackwater fever as readily as Europeans, if they are exposed to the same conditions.

Plehn mentioned serious outbreaks of blackwater fever among negroes on the Cameroon mountains, those who come to the coast from the interior being especially attacked.

Other predisposing causes are debility from previous illness, bad food, hardships of all kinds, dysentery, etc. It has been stated again and again that Europeans are rarely attacked within the first year of residence in a blackwater-fever country, though cases have been reported after so short a residence as three or four months, and exceptional attacks may develop in those who have not previously shown definite symptoms of malaria.

Of a similar nature is the dramatic occurrence of blackwater fever in apparently healthy persons who have arrived in England at the expiration of their duty, or on leave. Instances of this kind have frequently come under the Editor's personal observation, and they may, or may not, be preceded by a typical attack of malaria; but as often as not the patient gives no previous history of fever while in residence on the West Coast of Africa, or elsewhere. The explanation of these cases appears to be that the subtertian malaria infection is lying latent[1] until aroused into activity by the exposure to cold, alcohol, or some other factor. Circumstances such as these invariably explain the occurrence of blackwater fever outside the endemic area.

It has been noted that this disease observes a rough seasonal incidence; it is especially frequent in late summer and in autumn in the southern states of the American Union. On the West Coast of Africa it appears to be most prevalent at the close of the rainy season, or in August and September; in Central Africa and Nyasaland, especially in the highlands, a maximal incidence is seen during the wettest months, May to August, when the lowest temperatures are registered. In Southern Rhodesia, where the hot rainy season and the dry cold season are sharply defined, the malarial incidence increases following the rains in April: that of blackwater fever immediately rises also, and is maintained from March to July. During the Great War, in Salonika and in Palestine cases of blackwater fever occurred among the troops solely during the cold winter months. This coincides, as has already been said, with the incidence of the disease in England.

Mechanism of hæmolysis.—The mechanism of the production of hæmoglobinuria in blackwater fever can only be given in rough outline, as there are various points that are not yet settled. A liberation of hæmoglobin into the plasma—hæmoglobinæmia—takes place, and can be demonstrated if the blood-serum is examined the moment the attack occurs; probably by the time hæmoglobin appears in the urine a large proportion of the red blood-corpuscles have already been destroyed. The hæmoglobin is thus excreted by the kidney, and causes the typical cylindrical plugs in the renal tubules, which represent coagulation of highly albuminous hæmoglobin-containing exudate. The hæmolysis is rapidly accompanied by the appearance of bilirubin and methæmalbumin (*pseudomethæmoglobin*) in the blood-stream, and this accounts for the characteristic icterus of the disease. At the onset of blackwater fever there is usually a sudden and noticeable contraction of the spleen, and it is possible that the hæmolytic substances are set free into the circulation from this organ, but the question still remains to be answered: what occasions this reaction—what pulls the trigger? It has been shown

[1] Subtertian rings are, in the Editor's experience, not infrequently encountered in new arrivals from West Africa, who have no fever, enlargement of spleen, or any clinical evidences of malaria.

that the administration of quinine may cause splenic contraction and may also cause destruction of a certain number of erythrocytes, but it certainly will not explain *every* case.

Nocht finds that quinine greatly intensifies the hæmolytic action *in vivo* of heterogeneous hæmolytic amboceptors, cobra venom and lysozithin, but has no effect on that due to toluylenediamine and phenylhydrazine. This effect was not seen in experiments performed in the test-tube. On the contrary, however, quinine assisted the hæmolytic action of lecithin in the test-tube, but not in the animal body. Nocht believes that the unknown hæmolytic substance of blackwater, when present in large quantity, can produce blackwater as a result of cold or over-exertion, but in smaller amounts the stimulating effect of quinine is necessary for it to bring about a hæmolytic crisis. Therefore three factors are necessary to produce an attack of blackwater: (1) an interior hæmolytic factor, the result of malaria; (2) lowered cholesterin content, so that the protective effect of this substance is decreased; and (3) quinine.

It has been shown by Neave Kingsbury, employing the van den Bergh reaction, that in 90 per cent. of cases of uncomplicated subtertian malaria the serum bilirubin is above the normal figure, which is taken as 0·5 units, and consequently urobilin derived from the serum bilirubin is found in pathological amounts in the urine of these cases. In blackwater fever and in severe subtertian malaria this excess of bile leads to bilious vomiting. Under normal conditions the reticulo-endothelial system of the body deals with the products of hæmolysis by splitting the hæmatin (the iron-containing part of hæmoglobin) into an iron-free pigment, bilirubin, and an iron-containing pigment, hæmosiderin. The bilirubin is excreted by the liver, resulting in an increased flow of bile. The enlargement of the spleen in malaria and in the blackwater-fever state may be due to the hypertrophy of the reticulo-endothelial system, and at the onset of blackwater fever the spleen is usually very large and tender. Normally, in a severe case of subtertian malaria there is hæmoglobinæmia, or the liberation of free hæmoglobin into the blood-serum, but this is immediately dealt with by the reticulo-endothelial system, while in blackwater fever the liberation of hæmoglobin is so extensive and so rapid that the renal threshold for free hæmoglobin is broken down and the pigment appears in the urine. It is important to realize that even when hæmoglobinuria occurs, most of the hæmoglobin is broken up by the usual mechanism and only a relatively small proportion—17 to 36 per cent.—is excreted in the urine.

According to Pearce, before the kidney will excrete hæmoglobin the blood must contain at one time more than 0·06 grm. of free hæmoglobin per kilo of body-weight, and moreover it has been ascertained that an amount equal to 17 c.c. of laked blood-corpuscles is necessary in order to produce hæmoglobinuria in man, so that it is possible to have a state of hæmoglobinæmia without hæmoglobinuria. It is apparently more a question of the rapidity with which hæmolysis takes place, rather than the degree.

Fairley and Bromfield have now shown, by quantitative methods, that methæmoglobin is the predominant pigment present in the plasma in this disease, and that it has an extracorpuscular origin from oxyhæmoglobin liberated during an intravascular hæmolysis of circulating corpuscles. In blackwater fever there is, firstly, hæmolysis of the corpuscle and, secondly, conversion of the liberated oxyhæmoglobin into methæmoglobin and methæmalbumin, and these facts render it improbable that the cause is a

true hæmolysin or direct drug effect on the corpuscle. A much more attractive hypothesis is that there is some derangement of metabolism associated with chronic subtertian malaria infection, which is precipitated by the administration of quinine or plasmoquine and gives rise to a potent hæmolytic substance which first lyses the corpuscles and secondly acts on the liberated oxyhæmoglobin.

Methæmalbumin is described as a new pigment in the blood in blackwater fever. This is a brownish pigment resembling methæmoglobin spectroscopically, but not reduced by Stokes's reagent or ammonium sulphide. Methæmalbumin (formerly known as pseudomethæmoglobin), being a non-threshold substance, never appears in the urine. It has been investigated by Keilin at Cambridge, who reports that it is a peculiar hæmoglobin derivative with a normal prosthetic group, but the globin portion of the molecule is undoubtedly modified. The spectrum has the general appearance of methæmoglobin with the bands shifted. Although it does not reduce with Stokes's reagent the compound contains a trivalent iron molecule. It can be produced artificially by the addition of serum to alkaline hæmatin, and has undoubtedly in the past been confused with it; and it has by no means yet been determined whether the pigment is, in fact, a combination of hæmatin and serum albumin.

Evidently the hæmolytic agent may be present in variable quantity in different cases, and at different stages of the same case. The plasma bicarbonate shows, usually, a definite increase, and a definite lowering of the alkali reserve is associated with urea retention in all cases, and clinical evidence of acidosis is developed, necessitating alkaline medication. Acidosis may develop in the absence of oliguria and ketonuria.

Of special importance in the genesis and prognosis of blackwater fever are the biochemical aspects as summarized by Ross (1932). Of these, probably the blood-urea is the most important; the amount of urea in the blood is invariably raised, especially in cases with threatened suppression of urine. Yorke, Murgatroyd and Owen have shown that the blood-urea commonly rises in uncomplicated cases of blackwater to 65 mg. per cent. on the fourth day of the disease, whilst in severe and toxic cases of subtertian malaria there is a tendency for a rise in blood-urea to take place; percentages between 27 and 52 mg. per cent. were recorded, and in one of the Editor's cases a figure as high as 207 mg. was recorded. Ross found in Rhodesia that the results in four cases of blackwater were within the normal range, and did not indicate in any way that an acidosis of the blood-plasma had taken place.

Dudgeon has shown that hæmolytic substances can be extracted from the tissues, and actually from the urine, in blackwater fever, and that similar substances can also be extracted from cases of subtertian malaria.

The analogy of the mechanism of hæmolysis in blackwater fever and in paroxysmal hæmoglobinuria—diseases which closely resemble each other in their general symptoms—has attracted a considerable amount of attention. It has been found that if the blood of a case of paroxysmal hæmoglobinuria be withdrawn and the serum separated, then cooled to freezing-point, and subsequently warmed to 37° C.

with the addition of the patient's erythrocytes, an active hæmolysis takes place. This does not occur in blackwater-fever cases. The test by which this fact is brought out is known as Yorke's autolytic reaction.[1]

The theoretical considerations which underlie this reaction are complicated, and concern the mechanism of immunity, the proportion of substances known as the immune body and as complement. In the serum of paroxysmal hæmoglobinuria[2] the immune body is greatly in excess of the complement, whereas in blackwater fever the reverse obtains.

Dacie, Isräels and Wilkinson have drawn attention to paroxysmal hæmoglobinuria of the Marchiafava type, the chief characteristics of which consist in anæmia of chronic hæmolytic type, associated with jaundice, and persistent hæmoglobinæmia. Autohæmolysis was demonstrated *in vitro* and shown to be dependent on the *p*H of the system. It has been shown that it is a nocturnal hæmoglobinuria, and that the urine is clear by day. The pigment is found to be methæmoglobin.

Symptomatology.—It is doubtful whether one can speak about an incubation period in blackwater fever, but it has been noted in Central Africa that an attack may occur eight days after exposure to malaria, and Arkwright and Lepper, in their series of cases, state that the maximal interval between the first recognized attack of malaria and the first attack of blackwater fever was ten years (in one case), and that the minimal period recorded was fifty days.

Some clinicians recognize a clinical condition which, for want of a better term, may be described as a *pre-blackwater state*. Sometimes a suspicion may be engendered that blackwater may be imminent, and it is wise to be on the look-out for the following clinical signs: The patient is one who has passed through several slight attacks of fever, or at any rate has been infected with the subtertian parasite for several months. The complexion is sallow, the conjunctiva icteric, the liver enlarged, congested and tender, the tongue furred, the spleen generally enlarged, and constipation is the rule. Persistent headache is usually complained of. The urine is dark, due to the excretion of urobilin, and contains a slight amount of albumin. On examination of the blood, scanty ring-forms of the parasite may be found, but it is a noteworthy fact that cases of subtertian malaria with high fever and large numbers of parasites in the peripheral blood do not, as a rule, develop blackwater.

The *onset* of blackwater fever is usually sudden. A slight or, more generally, a very severe rigor is followed by intermitting, or remitting, or irregular fever with marked bilious symptoms. The pyrexia and rigors do not seem to be the effects of the malaria parasites as much as of the sudden liberation of the products of

[1] (1) Blood placed in incubator at 37° C. at once; no hæmolysis. (2) Serum kept at 0° C. for 5–7 mins., then in incubator for an hour with erythrocytes; hæmolysis. (3) Serum kept at 0° C. for an hour, then in incubator with erythrocytes; little hæmolysis.

[2] Donath and Landsteiner have shown that in this disease hæmolysis takes place in the peripheral blood, and that cold is the exciting cause.

hæmolysis. In other words, it is a kind of "protein shock." Earlier or later in the attack, usually during rigor, the patient becomes conscious of aching pain—perhaps severe—in the loins, in the region of the liver and spleen, which are enlarged and palpable, and over the bladder. In exceptional instances these local pains are absent. In consequence of a somewhat urgent desire he passes water, when he is astonished to see that his urine has become very dark in colour, perhaps malaga-coloured or, possibly, almost black. The fever continues, though it is not necessarily very high. Very likely he suffers from epigastric pain and distress, bilious vomiting to an unusual extent and, it may be, bilious diarrhœa; or he may be constipated. The pain in the loins and the liver-ache continue, and the urine becomes darker and darker. By and by the sufferer breaks into a profuse sweat, and the fever gradually subsides. The urine, which hitherto may have been very abundant, or perhaps somewhat scanty, now flows freely; and after passing through various paling shades, from dark brown to sherry red, becomes once more natural in appearance. Usually, and coincidently with the appearance of the dark colour in the urine, or even before this has been remarked, the skin and scleræ rapidly acquire a deep saffron-yellow tint. This icteric condition persists and even deepens during the progress of the fever, continuing for several days to be a striking feature in the symptoms. Occasionally bile-pigments are present in the serum; more usually free hæmoglobin can be demonstrated spectroscopically. When the fever subsides the patient is conscious of a feeling of intense weakness, from which he recovers but slowly. Fever, with or without rigor, may recur next day, or for several days; or it may cease; or it may be remittent, or almost continued, in type. The hæmoglobinuria may recur with each rise of temperature, or there may be only one or two outbursts; it may continue for an hour or two only, or it may persist, off and on, for several days or even weeks.

In the more severe form of hæmoglobinuric fever there is usually a very great amount of bilious vomiting, of intense epigastric distress, and of severe liver- and loin-ache. The urine may continue copious and very dark in colour; or, continuing hæmoglobinous, it may gradually get more and more scanty, acquiring a gummy consistence, a few drops only being passed at a time. It is considered that the kidneys may excrete up to 36 per cent. of the total hæmoglobin in the blood, though this by no means represents the total amount liberated in many cases of blackwater fever. Finally, urinary excretion may be completely suppressed.

In severe cases death is the rule. It appears to be brought about in one of three or four ways. The fever may assume the typho-adynamic type; or suddenly-developed cerebral, hyperpyrexial, or algid symptoms may supervene. Hiccough is a fatal symptom. In other cases the symptoms may be like those consequent on sudden and profuse hæmorrhage—jactitation, sweating, sighing, syncope.

Death may take place from sudden heart-failure after slight exertion, or from exhaustion consequent upon cyclical vomiting, or from sudden hæmorrhage from stomach or bowel. Or it may be that suppression of urine, persisting for several days, terminates, as cases of suppression usually do, in sudden syncope, or convulsions and coma. More rarely, nephritis may ensue and the patient die from uræmia three or four weeks after all signs of hæmoglobinuria and fever have disappeared. Some superimposed infection, streptococcal, septicæmic, or pneumonic, may ensue and be the cause of death some weeks after apparent recovery. One attack of blackwater appears to predispose the individual to a second, and second attacks, or more than two, have been noted in Nigeria in about 20 per cent. of cases; according to Stephens, sixteen is the largest number recorded. It is necessary to lay special stress on these points, for when a man has suffered and recovered from two attacks, the third is generally fatal.

Blackwater fever is highly dangerous to pregnant women, during parturition or during the puerperium. Particular care should always be taken to guard women in these circumstances from malaria, especially in districts in which the subtertian parasite is most prevalent. Their blood should be frequently examined and they should take prophylactic courses of atebrin from time to time. In the literature reports of such cases are rare. Thomas and Miller relate a remarkable case of blackwater during pregnancy of the thirtieth week with delivery of a dead fœtus in the middle of the attack. The patient's life was saved by repeated blood and drip transfusions and the case was still further complicated by a severe attack of bacillus coli pyelitis.

Sequelæ.—Anæmia and debility are the common sequels of a blackwater-fever attack, but usually, under hygienic conditions, the recovery of the patient to normal is astoundingly rapid. A curious sequel is cholelithiasis, owing to the formation of pigmented biliary calculi from inspissation of bile in the gall-bladder. K. D. Fairley originally drew attention to this phenomenon in a case of blackwater fever in Australia, and the Editor has since had two cases in which this was noted three weeks after the cessation of blackwater and in which the pigmented calculi were demonstrated at operation.

The urine.—If the characteristic dark-brown, generally acid, urine of a hæmoglobinuric case be stood for some time in a urine glass, it will separate into two well-marked layers; an upper of a clear though very dark port-wine tint, and a lower—perhaps amounting to one-half or one-third of the entire bulk—of a somewhat brownish-grey colour, and consisting of a sediment in which an enormous number of hyaline and hæmoglobin tube-casts are to be found, together with a large quantity of brownish granular material. Epithelium is also met with. Blood-corpuscles may be entirely absent, or very few in number. With the hæmoglobin there is also an escape of the serum-globulin of the blood, for the urine, in many cases, turns almost solid on boiling. The precipitated albumin carries down with it as it sub-

sides the dissolved and suspended hæmoglobin, leaving a pale-yellow supernatant urine. For some days after the urine has regained a normal appearance it will still contain albumin, though in gradually diminishing amount. Spectroscopic examination gives the characteristic bands of oxyhæmoglobin, as well as those of methæmoglobin. The appearance of oxyhæmoglobin is usual in very severe or fatal cases, methæmoglobin in the less severe or mild, in which the prognosis is more favourable. After the disappearance of the blood-pigments, urobilin can usually be demonstrated in pathological amounts.

Eye complications.—Hæmorrhages into the retina sometimes occur during the course of blackwater, and the Editor has seen a case of altitudinal hemianopia where there was total blindness in the lower half of the visual field.

Mortality.—This varies greatly in different epidemics, in the same and in different places, and under the same treatment. Some cases are so mild and transient, amounting, perhaps, to a single emission of hæmoglobinous urine, with little or no fever, that they are unattended with risk; on the other hand, a practitioner may encounter a run of severe cases in which nearly all die. Some old residents in Africa have passed through ten or more attacks with impunity. In Southern Nigeria and in Algeria the case-mortality has been as high as 50 per cent., but, as a general average, it may be put down as about 25 per cent.

Sequelæ of malaria.—The term *malarial cachexia* is applied to a group of conditions, more or less chronic, believed to be the result of an antecedent attack of severe malarial fever, or of a succession of such attacks, or of prolonged exposure to malarial influences.

The leading symptoms are those of anæmia, characterized by the peculiar sallowness of the skin, yellow sclerotics, enlargement of the spleen and, it may be, of the liver as well. As a rule, the subjects of cachexia are liable to frequent and irregular attacks of fever, though in highly malarious countries it is not unusual to see cases in which fever has never been a feature, or it may have been very mild in character. In such countries a large proportion of the population have enormously enlarged spleens, causing great protrusion of the abdomen, together with much emaciation and dry, rough skins. It is said that in some intensely malarial countries children are occasionally born with enlarged spleens; in rare instances they are infected through the mother *in utero* but it is probable that in most cases they become inoculated with parasites immediately after birth (*see* p. 62).

In the young the general growth of the body is stunted and puberty retarded, and abortion and sterility are common effects of malarial cachexia in adults.

The spleen may become so enlarged under repeated attacks of the congestion attending a succession of fever fits, or in consequence of a less active

and perhaps feverless hæmolysis, that it may come to weigh many pounds, and so to increase in bulk as to occupy nearly the entire abdomen. The capsule of the gland, particularly on its convex surface, is thickened, and perhaps the seat of fibrous patches, or even of adhesions to neighbouring organs. Many of the trabeculæ forming the framework of the gland become greatly hypertrophied. On section, the tissues of such a spleen are found to be moderately firm, and usually of a reddish-brown colour; but when death happens soon after or during a febrile attack, section of the gland shows a dark surface from deposit of hæmozoin, the pulp at the same time being softened. Perhaps from over-distension, some of the vessels in the interior of the gland give way, and then there is a breaking-down of the spleen pulp in patches, the remains of splenic tissue floating about in the extravasated blood.

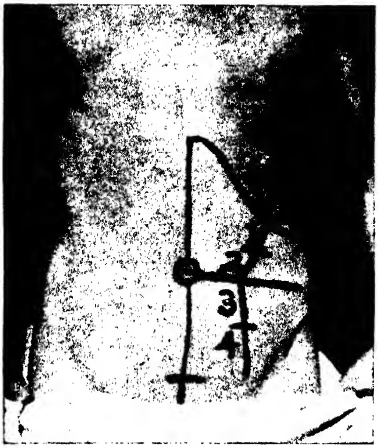


Fig. 8. Schüffner's method of determining degree of splenic enlargement. (*After Dr. L. W. Hackett.*)

"*Splenic index.*"—There are practical points in connection with malarial spleen which deserve mention. The relative absence, or prevalence, of these enlarged spleens or "ague cakes" in the native population is an excellent rough indication of the salubrity or the reverse, as regards malaria, of any particular district. Wherever they are common the district is malarious, and therefore unhealthy, perhaps to Europeans deadly, and should be looked upon as extremely unfavourable for either camping or residential purposes.

Another practical point is that these enlarged spleens are easily ruptured by a blow on the belly; this fact must be remembered in administering even mild corporal punishment to natives of malarious countries. Splenic ruptures are, of course, unless immediately operated on, generally fatal. Occasionally the spleen may rupture spontaneously owing to rapid increase in size in the course of an attack

of fever; but splenectomy does not necessarily eradicate the malarial infection from the body.

In estimating the amount of malaria in a community the "splenic index" has been found to be most reliable. In other words, children between the ages of two and ten form the only safe guide (Stephens and Christophers), for among the inhabitants of a very malarious country the adults are more or less immune and their spleens are diminished in proportion. The infantile spleen rate *per cent.* is the basis of the endemic malariousness of a locality. It is necessary to guard against the tendency to over-estimate the value of the splenic index. Barber, in the Philippines, working with children 5–10 years

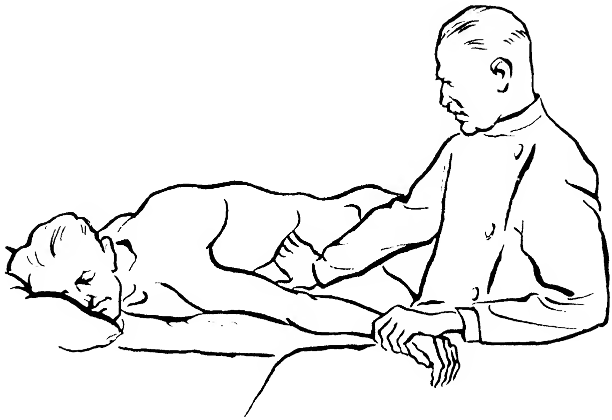


Fig. 9.—Method of spleen palpation. (*After Scholler; Munch. Med. Wochenschr.*)

of age, obtained a splenic index of 13.3 and a parasite index of 11. Wilson and Clark, in a survey of 1,100 Haitian labourers and 2,007 school-children between 6 and 14 years of age, found that the parasite-rate, determined by the thick-film method, was of far greater value in estimating the prevalence of malaria than was the splenic index. Of 11,000 adults 23.5 per cent. had positive blood-films and 3.03 per cent. had palpable spleens: of 2,007 children, 50.52 per cent. had positive blood-films and 3.03 per cent. palpable spleens.

The degree of splenic enlargement may be measured with the child standing up or lying down. Considerable differences in the results obtained are given by the two methods, higher values being obtained in the recumbent position. In India and in the tropics generally where gross degrees of enlargement are commonly encountered, the standing position is nearly always used. The best method is for the child to be drawn gently across the observer's knee, the hand being inserted beneath the scanty clothing and pressed against the costal margin while the child is told to take a deep breath. The degree of splenic enlargement is usually classified in finger-breadths below the

costal margin. Obviously this method is liable to fallacies. The distance from the costal arch to the pubis is very different in an infant of two years and a child of ten. Christophers has devised a method by applying to the actual measurement from the costal margin to the apex of the enlarged spleen a correction based upon the nipple-umbilicus length of the child.

In the average Indian child of six years of age the four-finger spleen reaches to the level of the umbilicus. In malaria surveys, the following classification is generally adopted :

Spleen-rate greater than 50 per cent. = Hyperendemic.
Spleen-rate 25 per cent. to 50 per cent. = Highly endemic.
Spleen-rate 10 per cent. to 25 per cent. = Moderately endemic.
Spleen-rate less than 10 per cent. = Healthy.

The child spleen-rate gives the measure of endemicity, the average enlargement that of intensity.

Schüffner's method of estimating splenic enlargement has many advocates : a line is drawn along the left costal arch and a second line parallel to the first is traced from the umbilicus ; these two lines are bisected by a third passing through the apex of the spleen (Fig. 8).

Occasionally an enlarged spleen has to be differentiated from a pathologically enlarged left congenital cystic kidney ; this has usually a rounded lower pole and a smooth round margin. An area of resonance can be elicited on its anterior surface, caused by the resonant band of the descending colon. The urine contains albumin and casts. Considerable care is sometimes necessary in the accurate palpation of the spleen. This is best done by using the radial aspect of the right index finger with the abdomen relaxed and the patient recumbent on his right side, with left arm extended (Fig. 9).

The parasite index is a simple percentage figure calculated from the number of persons actually showing parasites in the peripheral blood at the time of examination. Figures for children and adults should be kept separate, as the spleen-rate falls with age more rapidly than does the parasite-rate, which shows how many adults of a community are really " healthy carriers."

The parasite-rate should always be obtained from the study of thick as well as thin films. From a study of curves prepared from splenic and parasite *indices* according to age, it is found that they run parallel to a remarkable degree. The parasite index as a sign of infectivity is more reliable up to five years of age, after which to the age of twenty-five it is on an average 10 per cent. less reliable than is the splenic index.

Changes in the liver.—Like the spleen, the liver in malarial cachectics becomes enlarged during accessions of fever. Under the influence of a succession of acute attacks, hepatic congestion may gradually acquire a more or less permanent character.

It is in livers of this description that a form of what is called *siderosis* is produced—a condition resulting from chemical changes undergone by the yellow pigment with which the various cells of the organ are charged. When first deposited, this pigment gives no ferrous reaction with ammonium sulphide, or with the double

cyanide of iron and potassium ; as the deposit becomes older, chemical changes ensue, resulting in the elaboration of a form of iron which will then yield the characteristic black colour with the former, and blue colour with the latter reagent. (See p. 70.)

Changes in the kidneys and the heart.—Changes similar to those found in the liver in the course, and in consequence, of malarial disease occur in the kidney ; in time they result in confirmed Bright's disease ; especially is this true in quartan infections. Hence, probably, the frequency of Bright's disease in some highly malarious climates. As a consequence of defective nutrition from prolonged anæmia and recurring fever, the muscular tissue of the heart in chronic malarials may degenerate, the ventricles dilate, and, in time, the lower extremities become œdematous.

Immunity in Malaria

In the course of malarial infection a certain degree of tolerance may develop.

In heavily-infected endemic districts, malaria is specially prone to appear in small children, and of these a proportion die early, while others acquire a degree of immunity through repeated reinfections. It has often been remarked that dark-skinned children having enormous spleens and a rich stock of malaria parasites in their blood, run about fever-free, and apparently in robust health. As these children grow up their immunity becomes stronger and, after twenty years of age, they may remain quite free from clinical signs, and even splenic enlargement may disappear.

It is accepted generally that malaria, like other protozoal diseases, differs from bacterial infections in that the causative parasites do not disappear but remain in the body, where a balance is established between the resistance of the organisms and the inherent tendency of the parasites to increase. Sergent, Parrot and Donatien have coined the term "*premunition*" to characterize the incompleteness of this immunity.

Taliaferro and his associates have assigned an important rôle to the reticulo-endothelium in this process. A parallel state of affairs has been found by Cannon and Taliaferro to obtain in birds infected with *Proteosoma*. Ziemann and others have endeavoured to distinguish between immunity to the toxins and that due to the parasites. In the latter case they disappear gradually from the body and the occurrence of a fresh infection is thereby rendered impossible.

It is well known that the negro in Africa, although he does get fever, does not get it so frequently or so severely as does the European, although the latter is less exposed to infection. Amongst the Malays Schüffner observed an immunity to the malaria parasites as described by Ziemann. Of the young children, 38 per cent. were parasite carriers, while in the older subjects it was as high as 50 per cent. The index in adults was 8–11 per cent. Of those examined, 92 per cent. showed enlargement of the spleen. Christophers

(1924) found the same conditions in India. In most districts in the tropics all three classical forms of the malarial parasite occur, and therefore immunity is produced against all three. In an untreated population, it is found that among children the benign tertian parasites disappear most quickly, the quartan parasites come next and the subtertian persist the longest. This is also the case among adults in whom the ring forms of the parasite predominate while the crescentic forms are very scanty. Several observers, including Blacklock and Gordon, have mentioned the presence of large numbers of subtertian parasites in the placentas from premature births and miscarriages, and malaria is undoubtedly the not infrequent cause of such mishaps. It is generally held that a racial immunity against malaria exists, or is acquired, by those races which have for generations been exposed to infection.

There are undoubtedly individuals who possess an innate immunity against malaria, even when they are residing in heavily-infected districts. It is usually asserted that the famous explorer Stanley was one of these. J. G. Thomson estimated that the process of acquiring tolerance to malaria demands continuous exposure for about fifteen years. Recent experiments by James and others with induced malaria seem to indicate that a certain degree of immunity can be acquired through hyper-infection, but that the immunity is not entirely specific even for a certain species, but only for a certain strain of parasite. Bagster Wilson has now shown that in non-immunes the subtertian parasite is monomorphic, characterized by minute rings and multiple cell-infection, whilst in immune persons the parasites are larger and polymorphic.

It is considerations such as these which may explain the sudden and severe outbreaks of malaria in endemic districts. No success has so far attended the efforts to demonstrate the actual presence of immune bodies in the blood of malaria patients. Sometimes meteorological causes combine to render conditions more favourable for the development of the transmitting anopheles with consequent increase and spread of the disease, as in the Ceylon epidemic of 1934.

Again, mass immigration from malaria-free districts may cause an outbreak of the disease, as in the case of the Panama Canal, and in the many outbreaks which occurred during the Great War. Subsequently the Greeks repatriated from Asia Minor suffered from serious epidemics with a high mortality in malarious endemic areas in Greece. The widespread malaria epidemic in Russia in 1920 could be traced, for the most part, to the migration of a half-starved population.

Sinton, who has given considerable attention to this aspect of immunity believes that there are two methods of attack upon the malaria parasite and its toxins, viz. (*a*) a cellular, and (*b*) a humoral one, and that these two factors are closely associated and act in combination.

The cellular factor is definitely established in the destruction of malaria parasites by macrophage cells. Primarily the host reacts to the infection by an increase in the number of these cells; later an active *specific* phagocytosis comes into being.

We are much less certain about the nature of the humoral factors ; in the case of acquired immunity there is certainly a development of specific antibodies and they are probably produced by the macrophage system as the result of stimulation of ingested parasites acting as a specific antigen. The element concerned may be a lysin, or possibly an opsonin. Antitoxic substances are also probably produced, and there is some evidence to show that a certain degree of passive immunity can be transferred by the injection of serum from an immune subject.

Diagnosis of the Four Clinical Varieties of Malaria

The recognition of the various forms of malaria parasite in the peripheral blood entails a knowledge of blood examination. For the details of this and of the methods of staining the blood the reader is referred to the Appendix, p. 1023. Some workers prefer the thick-drop method (Appendix, p. 1021) as offering a more certain chance of discovering the parasites when they are scanty in the peripheral blood, but it is by no means such a certain method of distinguishing the species of parasite.

Bearing of quinine, atebrin and other drugs on microscopical diagnosis.—It is of little use to examine the blood for the intracorpuscular forms of the malaria parasite after full doses of quinine have been taken ; the drug rapidly brings about the disappearance of this phase of the parasite. The crescent, or gametocyte, of the subtertian parasite is alone unaffected by quinine, and in suitable cases may be found for weeks after the patient is cinchonized ; on the other hand plasmoquine has a selective action on this form (*see* p. 115). Changes in the red blood-corpuscles are sometimes of assistance ; a definite increase of the large mononuclear cells above 15 per cent. is suggestive.

Gordon Thomson and others have suggested that a complement-deviation test, using an emulsion of an organ rich in parasites, as well as artificial cultures of the plasmodia as antigens, may prove to be a distinct aid to diagnosis.

About 28 per cent. of malarial bloods in the acute stage of the disease, when parasites are plentiful in the peripheral blood, give a positive Wassermann reaction ; but this is not so in either the chronic or the quiescent stage, a fact which has to be borne in mind in excluding syphilis in a malarial subject. Saunders and Turner (1935), who have reviewed this subject, believe that these reactions are not strictly specific, but that malaria in the acute stage gives rise to anticomplementary reactions.

Diagnosis of malaria by the therapeutic action of quinine.—It is unfortunately true that, in countries where malaria exists, any case of fever is diagnosed as such, and the practitioner may be called in only when a considerable amount of quinine has been taken and has failed to achieve the desired results. Unfortunately, too, a good many practitioners are in the habit of relying unduly upon the therapeutic action of this drug, without verifying their diagnosis by microscopic examination.

Diagnosis from clinical signs.—The most important clinical sign is periodicity of the fever, which occurs in its most typical form in the tertian and quartan infections; in the subtertian, however, the fever may be most irregular, and there may be no pyrexia at all.

Enlargement of the spleen is a common clinical sign in all forms of malaria. In old-standing infections it may be very large indeed, and occupy the greater part of the abdominal cavity ("ague cake"), but in early, and it may be very severe, cases the spleen may not be sensibly enlarged at all, and it therefore fails entirely as a clinical guide: usually, however, in the absence of splenic enlargement, splenic *pain* is often present during the attack. Moreover, the patient may be suffering from some totally different disease, and the palpable spleen may be the result of a long-standing malaria infection quite unconnected with the attack in question.

To the clinician accustomed to many cases of fever, the general appearance of malaria patients, the bright glistening eye, set in rather a dusky orbit, contrasted with the pale and ochreous complexion, combine to create an almost diagnostic appearance.

Goldfeder (1936) describes an eye symptom both in latent and chronic malaria. The vessels are superficial, and in fact appear as if raised above the surface of the ocular conjunctiva; they are of a larger calibre than the other conjunctival vessels, and are darker in colour than other surface vessels. When the eye is directly forwards they have a wavy outline.

Diagnosis by the patient's history.—A suddenly developed fever arising in a previously healthy person who has recently arrived from a malarious country usually turns out to be a case of malaria fever. In instances of this kind the patient will generally give a history of similar attacks while resident abroad, but there are exceptions to this rule, for, occasionally, residents of tropical countries may develop their first attack of malaria shortly after arriving in a cold climate, and this attack, aggravated by the conditions, may run a very severe course; this is especially the case with recent arrivals from the West Coast of Africa, and it is true for both benign tertian and subtertian infections, the parasite lying dormant in the blood-stream, it may be as long as eight months and, in the case of the former, one year or more.

An actual description of the febrile attack itself may be suggestive. The rapid rise of temperature, the history of the cold, the hot, and the sweating stages, the rapid defervescence of the fever, and the subsequent sense of well-being, are more characteristic of a malarial attack than of any other febrile disease. At times periodicity is a trustworthy enough clinical test. *Tertian and quartan periodicity occur only in malarial disease.*

Henry's sero-flocculation test.—From an examination of two kinds of pigment derived from hæmoglobin—the ochre-coloured ferruginous pigment

and the melanin—it was considered probable that pigments would produce antibodies in the blood of diagnostic importance in the form of a flocculation test. Accordingly the ferro-flocculation and the melano-flocculation tests were devised.

Malarial sera give flocculation reactions with *metharfer*—albuminate of iron with suspension of melanin. A series of six test-tubes are set up, each containing 0·2 c.c. of test serum. To each tube in serial order add 1 c.c. of the reagents: 1 : 450 metharfer in distilled water, 1 : 4800 albuminate of iron, 1 : 6000 albuminate of iron, 1 : 4800 albuminate of iron in 1-in-1000 salt solution, and 1-in-1000 salt solution as a control. The tubes are placed in the incubator at 37° C. for 1½ hours. In other tests a melanin suspension alone is used. The melanin is obtained from the choroid of an ox's eye, which is scraped and ground up with twice its volume of distilled water, formol being added as a preservative. It is then filtered through lightly packed glass-wool, centrifuged for eight minutes at 4,000 revolutions.

The suspension is kept in sterile tubes in the ice-chest and left for one month to become stable before use. The results are read with a Vernes-Bricq-Yvon photometer. The flocculation is said to persist long after the disappearance of the parasites and other signs of malaria.

Benhamou and Gille think that the reaction depends upon an increase in the euglobulin in the serum and diminution of cholesterin-serum-albumin. Brandt and Horn, using albuminate of iron, consider that a positive result is obtainable in inoculated malaria. The final results recorded in Georgia in a large series of malaria cases are somewhat indefinite (Gnochvili and Keigueloukhes). Proske and Watson (1939) have investigated this method anew and have endeavoured to make the test more generally adaptable, using the tyrosin-chromogenic index in place of the photometer. In normal blood sera they find that the tyrosin index for euglobulin fluctuates between 50–80, whilst that for serum from malaria patients ranges from 80–280, or higher. The test is non-specific, but its high sensitivity in malaria promises to make it a useful adjunct in laboratory diagnosis. Actually, the test was found to be indicative of the presence of malaria in 97·4 per cent. of known cases examined, compared with 81·9 per cent. positive thick films.

Wolff (1939) has elaborated a new modification which dispenses with elaborate apparatus. This is the Buffer Precipitation Test (B.P.T.), which represents a further modification of Chorine's method. *B.P.T.* aims at the precipitation of euglobulin under stabilized conditions of buffer solutions arranged in sets of different *p*H concentrations. It is claimed that the diagnostic value is at least as high as that obtained by other serological malaria tests.

Diagnosis by splenic puncture.—According to Knowles, Acton, and das Gupta, the spleen appears to function as the grave rather than the birthplace of the malaria parasite; therefore spleen puncture may, exceptionally, be used as a method of diagnosis especially in chronic and relapsing cases due to the benign tertian parasite. In films from such a puncture the observer sees malarial pigment, both free and intracorpuscular, and remains of malaria parasites undergoing disintegration. The recent experiences of Foy and Kondi in this direction in Macedonia have proved disappointing.

Provocative methods of diagnosis.—It has been noted, particularly by Italian observers, that exposure to undue fatigue or cold is apt to bring on an acute attack of malaria fever in latent cases, thus rendering detection of the parasites in the peripheral blood comparatively easy. It is suggested by some, though to others it may not appear justifiable, that a patient in whom malaria is suspected should be made to climb a high mountain and expose himself to cold at a considerable altitude, in order to provoke an attack.

There are other methods which have been employed in order to cause the parasites to appear in the peripheral blood; such are the subcutaneous or muscular injection of normal serum or other substances producing protein-shock, with strychnine, nitroglycerin, iron, ergotin, pituitary extract or adrenalin. The intravenous injection of salvarsan is sometimes followed by a similar result. X-rays applied to the spleen, and ice-packs to the abdomen, are other provocative methods. It is said that the most efficacious measure is the intravenous injection of 2 c.c. of adrenalin hydrochloride dissolved in 300 c.c. of normal saline, and that this procedure results in the immediate reduction of an enlarged spleen, with the appearance of the parasites in the peripheral blood (*see* Ascoli's method, p. 114).

De Langen and others have shown that the number of parasites in the peripheral blood may be greatly increased after exercise, a process which drives the parasites out of the blood reservoir in the internal viscera where they tend to accumulate.

Differential Diagnosis of Malaria and of Blackwater Fever

The differential diagnosis of malaria entails a knowledge of all fevers, both tropical and non-tropical in origin; but there is one point to be borne in mind, for which there seems to exist at present no adequate scientific explanation, namely, that in patients who have suffered for some time from recurrent malarial attacks, the temperature of a subsequently contracted febrile disease, for example measles, may show a periodicity foreign to its usual character.

In hepatic abscess, although the liver is enlarged the spleen is not necessarily so. In hepatic abscess the fever occurs generally, though not invariably, in the late afternoon or evening.

In bilious remittent malaria the icteric tinting of the skin is an earlier feature; albuminuria is not so common and generally not marked; temperature is maintained high for many days, not subsiding in three or four days as in yellow fever.

Many of the diagnostic difficulties which formerly existed have been obviated by the introduction of modern methods.

Without the microscope it is sometimes impossible to differentiate typhoid types of malarial fever from genuine enteric in the early stages.

The following, also, are often mistaken for malarial fever: Cerebro-spinal meningitis; fever of urinary origin (sometimes renal calculus); the fever attending the passage of gall-stones, or inflammation of the gall-bladder; that associated with pyelitis and surgical kidney; perineal abscess; lymphan-

gitis, particularly that form associated with elephantiasis and other filarial diseases; undulant fever; relapsing fever; trypanosomiasis; kala-azar; the fever associated with tuberculous disease, with ulcerative endocarditis, with some types of pernicious anæmia, with splenic leucocythæmia, with visceral syphilis, with pulmonary carcinoma, with rapidly growing sarcoma, with forms of hysteria, and with many obscure and ill-defined conditions.

Differential diagnosis of special forms of subtertian malaria.—As has already been indicated, there is a natural tendency for medical men unacquainted with the clinical forms which subtertian malaria may assume, to diagnose its various symptoms as manifestations of some other disease. Even surgical conditions, such, for example, as appendicitis or other acute abdominal disorders calling for urgent operative interference, may be suspected. The following statement is based upon actual diagnoses which have been made on clinical grounds alone, without the confirmation of a microscopic examination, but which subsequently proved to be cases of subtertian malaria:

(*a*) *Cerebral forms* of subtertian malaria are apt to be mistaken for sunstroke, heatstroke, mental derangement, hysteria, alcoholism, aphasia, convulsions, epilepsy, cerebro-spinal meningitis, or even plague.

(*b*) *Abdominal forms*, for dysentery, both amœbic and bacillary, cholera or paracholera, intestinal obstruction, appendicitis, biliary colic, cholecystitis, hæmorrhagic pancreatitis, or liver abscess. Malarial appendicitis can be distinguished on clinical grounds by overcoming the muscular defence by patient palpation, from the subsequent passage of fæces and flatus, the dicrotic, full pulse, the flushed facies, and the rapid fall in temperature following upon a profuse sweat.

(*c*) *Pulmonary forms*—i.e. malarial pyrexia with pulmonary congestion and myocarditis—for bronchitis, pneumonia, and pleurisy, especially on the left side (due to congestion of spleen), disordered action of the heart or even valvular disease.

(*d*) Those with *cutaneous petechiæ*, for measles, endocarditis, or purpura.

(*e*) The *febrile* cases with remittent pyrexia, for influenza, rheumatic fever, enteric, phlebotomus fever, trench fever, paratyphoid, or relapsing fever.

(*f*) The *icteric* cases, for yellow fever, Weil's disease, or infectious jaundice.

(*g*) The *cachectic* cases, for acute nephritis, pernicious anæmia, splenomedullary leucocythæmia, debility, or pulmonary tuberculosis.

(*h*) *Œdematous forms*, exceptional cases with general anasarca, ascites, and polyuria, may be mistaken for beriberi; a general œdema may be the only outstanding sign in a heavy subtertian infection.

Differential diagnosis of blackwater fever.—The diseases with which blackwater fever might be confounded are—(1) paroxysmal hæmoglobinuria; (2) bilious remittent malaria; (3) yellow fever; (4) infectious jaundice. If it be borne in mind that rigor, hæmoglobinuria, pyrexia, are all in evidence at the outset in blackwater fever, and also that blackwater fever is acquired only in certain countries, an error in diagnosis is improbable.

Prognosis of Malaria and of Blackwater Fever

As a general rule, **malaria** is a much more serious disease in children than in adults, and its attacks are more marked in women than in men. It is a serious disease in the weakly, especially in those whose constitutions are undermined by any intercurrent disease, such as phthisis or dysentery. It may lead to abortion in pregnant women, and the possibility of such an occurrence must always be reckoned with.

Prognosis of blackwater fever.—A severe attack of blackwater fever generally rids the patient of his present malaria infection, but, as the result of this very exhausting illness, his general health suffers for some time afterwards. Patients who have passed through one attack should not be permitted to return, for a year or more, to an endemic centre of the disease. The course of a particular attack can, generally speaking, be judged by the severity of its onset. So far from protecting against future attacks of blackwater fever, the patient appears to be predisposed to this condition. Therefore, those who have survived two attacks should not be permitted to return to the tropics ; a third often proves fatal.

Apparently mild cases in which fresh paroxysms occur are of grave import. Anuria usually indicates a fatal termination.

TREATMENT OF MALARIA

General management of a case of malaria.—Every case of malaria with fever should be nursed in bed and treated seriously, for severe symptoms may develop at any moment. It is especially important that the patient should not be left alone in a room, particularly in subtertian infections, as he may become maniacal and may take his life. The room should be darkened to mitigate the photophobia and the wearing of a sports shade or an eyeshade serves this purpose very well.

Special attention should be paid to the patient's clothing ; his feet must be kept warm with bed-socks, and during the stage of perspiration the bedclothes should be frequently changed. Attention to the food is also necessary. During the acute stages it is best to give plenty of water and lemonade to drink, while the food itself should be fluid and easily digestible. During the convalescent stages, if the patient has an appetite, full diet should be substituted, and there is no point in denying to patients who are used to it a strictly moderate amount of alcohol ; beer and stout in moderation are useful.

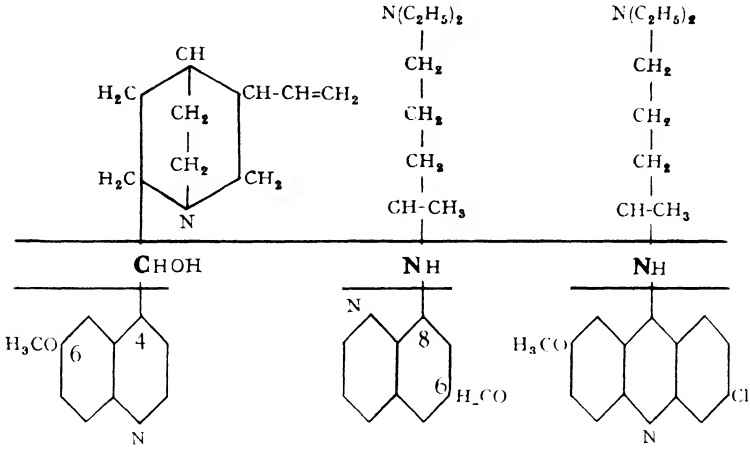
For three hundred years it has been almost universally believed that in quinine medical science possessed a genuine and specific remedy for this fever—a remedy unrivalled throughout the whole range of medicine in its potency and effects ; but during the last ten years, synthetic specific remedies—plasmoquine and atebrin—which equal, in some respects, quinine, have been produced.

It is convenient, at this point, to record the formulæ of these specific drugs, which may be roughly divided into a ring system, a connecting link, and a basic component.

I. Quinine Treatment

Quinine hydrochloride is the form which should be used by preference; it may be obtained in tablet form, and taken well crushed up in water; *the bitter taste is quickly removed by masticating a piece of bread.*

Quinine sulphate pills are to be avoided, as they often pass through the intestinal canal without being absorbed. For this reason *sugar-coated tablets are not recommended for use in the tropics.* Ten



$C_{20}H_{24}O_2N_2$ — **Quinine** | $C_{19}H_{29}ON_3$ — **Plasmoquine** | **Atebrin**

grains of the quinine sulphate is rendered soluble in distilled water by 10 minims of acid. sulph. dil., or acid. phosph. dil.

Method of disguising taste of quinine.—In order to disguise the disagreeable taste of quinine, which is so objectionable to some people, syrup of orange or glycerin (1 dr.) may be added. Quinine is rendered less bitter if mixed with milk. A preparation known as *Lacquin* is made by Cow and Gate Ltd. This is well tolerated by some people and the Editor has had good results from its use. The modern preparation is a powder containing quinine ethyl carbonate gr. 2½ to one teaspoonful of milk powder, flavoured with vanilla.

Quinine-Weil is said to be free from the bitter taste of quinine and in action similar to quinine hydrochloride. According to Vigoni, who has used it on the Belgian Congo, it is suitable for infants and native children. It contains 60 per cent. of quinine base and its formula is given as $C_{20}H_{24}O_2N_2C_{16}H_{11}O_2N$. It is given in the same doses as quinine.

Dosage of quinine.—The maximum dose of quinine for an adult European is somewhere in the region of 30 gr. (2 grm.) per day. For some infections 20 gr. suffices. Hitherto, on the whole, in the tropics there has been a tendency rather to over- than to under-dosage. With prolonged quinine treatments it is not advisable to give more than 10 gr. a day.

For children about one-twentieth of the adult dose for each year of age is recommended, so that a child of five years would receive one-quarter of an adult dose. Beyond fifteen years of age the dose is that of an adult.

Quinine amblyopia is generally the result of intense quinine poisoning after a dose of 80–160 gr. In exceptional cases, with an idiosyncrasy to the drug, temporary blindness has followed even moderate doses. Other symptoms, such as mental confusion and coma, may accompany the amblyopia.

Quinine idiosyncrasy.—It has been pointed out by Dawson and Garbade that an indication of this state may be obtained by the scratch test (endermic test of idiosyncrasy). A scratch is made on the flexor surface of the forearm and a drop of 1-in-10 solution of quinine applied. Œdema with a zone of erythema will result if the test is positive, and a saline control should be made at the same time. It has not been found possible to desensitize by this method: in fact the subjects appear to become even more sensitive.

Quinine in pregnancy.—Care should be exercised in giving quinine to pregnant women, for undoubtedly, if administered in large doses, it may sometimes cause miscarriage. The fact of pregnancy, however, must not debar the use of the drug altogether; only, in such circumstances, it should be given in the minimum dose likely to be effectual, say 3 gr. repeated every eight hours for two days. *A pregnant woman will run more risk of miscarriage and of detriment to her health from repeated ague fits than from a reasonable dose of quinine.* Indeed, Acton concluded from his pharmacological studies that miscarriage can only be brought about by doses of quinine sufficiently large to poison the patient.

Taken in prophylactic doses it does not interfere with menstruation, conception or pregnancy. The Editor has shown that plasmoquine compound is well tolerated by pregnant women, and the administration is not attended by undue risks (*see* p. 117). There is no satisfactory evidence that quinine has any effect on menstruation, although Cook is of the opinion that it increases the amount of flow.

Quinine in the puerperal state.—It is a wise precaution in malarious countries to give a few 5-gr. doses of quinine during labour or soon after. The puerperal state seems to have the effect, as any other shock or physiological strain might, of waking up the slumbering malaria parasite. A dose or two of quinine in these circumstances does no harm, and may, by choking off a threatening fever, avert suffering and anxiety, and even danger.

Excretion of quinine.—Nierenstein's observations show that the

excretion of quinine is the same by whatever route it is administered. The drug appears in the urine within fifteen minutes, and altogether one-quarter of the total quantity is passed in this manner, the highest concentration being 7–11 gr. quinine base per litre (*see* Appendix, p. 1028). Large amounts are also excreted in the fæces.

Foy and Kondi use Wagner's reagent for the detection of quinine in the blood, while Vedder and Masen have still further improved the colorimetric method by introducing the gum-ghatti and potassium iodide indicator.

Excretion of quinine in milk.—Quinine, even in prophylactic doses, is excreted in the milk of nursing women. In order to demonstrate this, 10–15 c.c. of milk is drawn off at intervals and added drop by drop to ten times its volume of 96-per-cent. alcohol containing 2 per cent. acetic acid, stood for half an hour, shaken and filtered. The amount of quinine in the filtrate is estimated by Tanret's reagent. Excretion commences in fifteen minutes and is completed in one hour.

Sinton's alkaline quinine treatment.—Sinton (1923) advocated a standard treatment for malaria in India. The patient is first given, as an aperient, hydrarg. subchloride 3 gr. followed by 1 oz. of magnesium sulphate dissolved in twice the amount of warm water. Should nausea or vomiting be present, the hydrarg. subchloride can be given in smaller doses with sodium bicarbonate. Two mixtures are given as follows :

(*a*) *Alkaline mixture.*		
Sodium bicarbonate	ʒi	(3·89 grm.)
Sodium citrate	gr.xl	(2·592 grm.)
Aq. dest. . . . . ad	℥i	(28·42 c.c.)
(*b*) *Quinine mixture.*		
Quinine sulphate	gr.x	(0·648 grm.)
Citric acid	gr.xxx	(1·944 grm.)
Magnesium sulphate . . .	ʒi	(3·89 grm.)
Aq. dest. . . . . ad	℥i	(28·42 c.c.)

Other forms of quinine.—*Euquinine or euchinine*, the ethyl carbonate of quinine, has the advantage of being almost tasteless, an important property in the case of children or fanciful patients, and, according to Fletcher, it is as effective as the more familiar salts of quinine. On the other hand, some tasteless preparations, such as quinine tannate, are useless, owing to their insolubility in water.

Quinine alkaloid is almost insoluble in water, but has in consequence less of the bitter taste than the more soluble salts, and appears to be absorbed from the intestinal canal.

Quinidine has an action upon the benign tertian parasite comparable to that of quinine.

Continuous drenching with quinine is of little use in persistent cases. It may be necessary, even in benign malaria, to give a course of intramuscular injections in order to cut short the fever. It has been found that cases of general paralysis treated therapeutically with inoculated malaria are extraordinarily amenable to quinine treatment.

Quinine given in regular dosage is known as anti-relapse treatment. Opinions differ as to the best course to pursue. It may be said that it is advisable to keep up the quinine for three months, either by the so-called week-end system, 30 gr. on each of two consecutive days, or 10 gr. once a day for six days.

If the spleen is tender, the application of a mustard plaster or a fomentation often gives relief. It is generally held that the absorption of quinine is greatly assisted by the administration of arsenic, and indeed in times of scarcity this drug has been administered in the routine treatment of disease. It is usually given in the form of liquor arsenicalis, 5 min. three times daily. The arsenic may be combined with iron in order to combat the anæmia, as in the following prescription :

Liq. arsen. acid.	♏iii	(0·178 c.c.)
Ferri sulph.	gr.ii	(0·13 grm.)
Acid. hydrochlor. dil. . .	♏iii	(0·178 c.c.)
Aq. dest.	ad ℥ss	(14·21 c.c.)

It may be more advantageous, especially during the convalescent stage of the disease, to prescribe iron and arsenic together in pill form, to which strychnine may be added, as in the following :

Ferri hypophos. . . .	gr.ii	(0·13 grm.)
Acid. arsen. . . .	gr. $\frac{1}{50}$	(0·0013 grm.)
Strych. hydrochlor. . .	gr. $\frac{1}{50}$	(0·0013 grm.)
Exc. . . .	q.s.	

Two or three of the pills are given every night.

Another method of prescribing arsenic is in the form of sodium cacodylate (sodium dimethylarsonate) in $\frac{1}{2}$- to 1-gr. doses hypodermically, as a general tonic and as an adjuvant to quinine.

Cinchona febrifuge (*totaquina*, or *quinetum*) is a preparation containing the total alkaloids extracted from cinchona bark, made in the Government factories in India and issued in the form of 3-gr. tablets. Owing to its cheapness it is much in use in that country ; it is especially useful in benign tertian infections, on account of the high percentage of quinidine it contains. The average composition of the cinchona febrifuge made by the Government of India is as follows :

Quinine	7·4	per cent.
Quinidine	22·83	,,
Cinchonine	18·58	,,
Cinchonidine	5·84	,,
Ash, etc.	45·35	,,

Thus it contains 54·65 per cent. of crystallizable alkaloids. The Java febrifuge contains 11·5 per cent. of quinine and a smaller percentage, 5 per cent., of quinidine.

Tebetren (methyl-hydrocuprein) is a preparation of quinine with an acridine dye and a derivative of cholic acid. The treatment consists of two tablets every four hours until 60 have been taken. Four courses are given with an interval of 3–5 days between each course. Its action is said to be more rapid than that of quinine alone.

Esanofele (in pill form) or *Esanofelina* (in solution) is a drug which has been much utilized in Italy; it comprises both arsenic and quinine. Each pill contains:

Quinine bisulphate . .	grm. 0·09	(gr. $1\frac{1}{3}$)
Arsenious acid . . .	grm. 0·0009	(gr. $\frac{1}{72}$)
Citrate of iron . . .	grm. 0·027	(gr. $\frac{2}{5}$)
Powdered herbs . . .	grm. 0·0145	(gr. $\frac{1}{4}$)

This is virtually what is known as Baccelli's mixture. The dose for a child under 6 years is two pills a day; from 7–14, four; for an adult, six; as a preventive it is recommended that two pills be taken every day. This preparation is sometimes recommended on the ground that it contains no quinine, but this is obviously a fallacy.

Mode of action of quinine.—The effect of quinine on the malaria parasites is not yet clear and it has yet to be proved whether it is direct or indirect.

The fact that malaria parasites, after the addition of quinine-saline solution of 1 : 10,000 concentration, are still infectious after twelve hours is strong evidence against the belief in direct action. On the other hand, tending to support the view that the effect is a direct one is the fact that torn or distorted parasites from which the nucleus is separated can frequently be demonstrated in quinine-treated cases: somewhat similar changes or "atebrin forms" have been observed after the exhibition of atebrin.

Many investigations have been devoted to the distribution of quinine in the blood and organs of the body; some consider that it is stored in the liver. Giemsa, for instance, thinks that the action of quinine is direct and that destruction of the parasites takes place in the endothelium of the vascular capillaries of those organs which accumulate quinine.

Probably, in *complete cure*, both actions come into play, and possibly *direct action* occurs first, as seen in the almost miraculous results of intravenous quinine injection. Furthermore, in ape-malaria it has been shown by Nauck and Malamos that the action of quinine is not interfered with if the main protective organ (*i.e.*, the spleen) is removed.

Whether administered by mouth, intramuscularly, or intravenously, quinine is rapidly absorbed and can be demonstrated in the urine within a quarter of an hour, whilst the rate of excretion varies very much and is largely dependent upon the amount and concentration of the urine. About 25 per cent. is excreted through the urine, 5 per cent. with the fæces, and smaller quantities through the saliva and the milk.

Toxic effects of quinine.—The milder effects are nausea, tinnitus aurium, dizziness, tremors and palpitations, and are shown by nearly all patients at the beginning of quinine medication. It is said that their absence indicates that the drug is not being absorbed.

Idiosyncrasies to the drug are encountered, while some people become hypersensitive from long-continued administration; some

develop cutaneous eruptions which may vary from a mild erythema to weeping eczema and even exfoliative dermatitis, and general œdema.

Local œdema of the eyelids, as well as of the nasal and oral mucous membranes, have also been observed. Cutaneous hæmorrhages approximating purpura with bleeding from the mouth, intestinal or urinary systems are met with, but are rare. Acquired sensibility to quinine is not infrequent, especially if the drug has been given in 15-gr. doses over a long period. If there are rises of temperature, this may be due to the quinine and not to the malaria, and such cases have to be carefully considered. If the quinine is discontinued the "fever" often disappears instantaneously.

Permanent deafness is rare after quinine therapy and occurs only if excessive doses are exhibited.

Some workers believe that in subtertian malaria the exhibition of quinine increases the production of crescents (gametocytes), but the recent experiences of Amies go to show that this is not really the case.

Another point requiring explanation is that quinine is more effective if withheld till the patient has passed through several attacks of fever; and that so-called quinine-resistant fevers are usually produced by chronic quinine intoxication.

Injection of quinine.—The *intramuscular* method is sometimes painful, and may be attended with some risk; but, in the circumstances, such possibilities count for little. As indications for intramuscular injection, the inefficiency of oral quinine, its non-absorption owing to severe vomiting or gastritis, the presence of severe, toxic, or pernicious symptoms, or of large numbers of parasites in the peripheral blood, may be taken as guides.

The most suitable readily procurable salt for injection is the hydrochloride or, better, the dihydrochloride, which is soluble in its own weight of water.

In giving an intramuscular injection, a stout, preferably platinum iridium needle, should be driven well home, deep into the gluteal muscles, the skin having been carefully cleansed. The solution must be freshly prepared and boiled, and the syringe and needle thoroughly sterilized. A syringe having a well-fitting glass piston and a plugging needle is the best instrument for giving these injections.

The dihydrochloride of quinine may be obtained in 5-gr. tabloids, specially prepared for intramuscular injection. Ampoules containing 9 gr. of quinine dihydrochloride to 2 c.c. of saline are on the market. One of these injections may be given into the buttocks daily for three consecutive days at the maximum.

When large numbers of intramuscular injections have to be given the quinine solution may be put up in vaccine bottles fitted with a sterilized rubber cap in a solution of 9 gr. of quinine hydrochloride in 1 c.c. of 0·75-per-cent. saline. The cap is disinfected and the needle of the syringe plunged through it into the bottle.

The best site for an intramuscular quinine injection is the gluteus maximus muscle at a point on a horizontal line with the apex of the great trochanter (Fig. 10.) This point, of course, is well above the exit of the deep-lying great sciatic nerve, which may be injured by plunging the needle in a false direction.

After the injection is made the part should be gently massaged so as to diffuse the solution, and the little wound sealed with collodion. *Quinine ought never to be injected into the neighbourhood of large nerves or blood-vessels, or be permitted to impinge upon the bone.*

It has been shown that a concentrated solution of quinine is rapidly absorbed from the tissues, and that its action upon the parasites in the circulation is almost instantaneous. There appears to be no special purpose in further diluting the quinine for the intramuscular route.

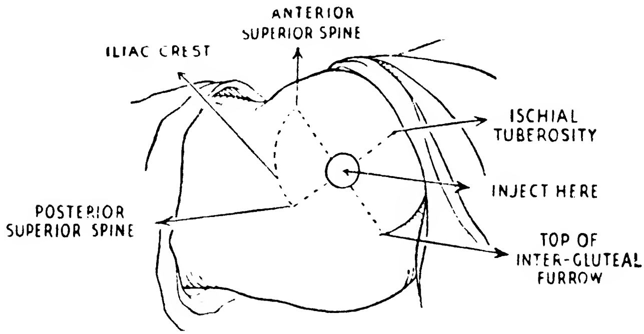


Fig. 10.—Diagram showing the site for a quinine injection.
(*Burroughs, Wellcome & Co.*)

From experiments on quinine solutions Martindale has suggested *mannitol quinine* as being the least irritating; the combination is as follows:

Quinine base	grm. 12·0
Boric acid	grm. 8·4
Mannitol	grm. 7·5
Distilled water to . . .	100 c.c.

1 c.c. contains 0·12 grm. (approx. 2 gr.) of quinine base and 0·084 grm. ($1\frac{1}{2}$ gr.) of boric acid.

This injection contains a reasonable therapeutic dose of quinine. In view of the work of Henry and Brown and others, the quinine in this form should be more potent against the malaria parasite.

Precautions.—It may be well to mention—not with the idea of deterring the practitioner from using the drug in this way, but to impress upon him the necessity for sterilizing the patient's skin at the place selected for injection and keeping instruments and solutions aseptic—that not only abscess, sloughing, and chronic painful indurations have sometimes followed the intramuscular injection of quinine, but also tetanus. (Fig. 11.)

A localized necrosis of the muscular fibres of the gluteus apparently occurs after every injection of quinine; this is followed by œdema and, it may be, a destruction of the blood-vessels, thus rendering the muscle a suitable culture-ground for the tetanus or other organisms which may, as we know, gain entrance through the blood-stream. The main point to remember is that this method has its *uses* as well as its *abuses*. There is no advantage in repeating the injection day after day in approximately the same spot; if

this is persisted in, extensive necrosis and hæmorrhage may result. In addition to tetanus and abscess-formation, gas gangrene and general streptococcal septicæmia have been observed. Injection into or near the great sciatic nerve has resulted in paralysis of the leg.

In the opinion of the Editor three intramuscular injections of quinine in the dosage advocated are quite sufficient to tide over the pernicious symptoms of malignant malaria and to save the patient's life. Continued pyrexia, however, does not necessarily indicate that parasites are still active in the tissues.

Fig. 11.—Quinine abscess of buttock, developing ten weeks after last quinine injection. (*Orig.*)

Quinine injections are often followed by the formation of fibrous nodules, the size of an almond, at the site of the injection. These persist for many years and give rise to a great deal of inconvenience; they may even break down and suppurate many years afterwards. The Editor has seen two such cases in which suppurating sinuses formed at the site of quinine injections given 25–30 years previously. In one case a suppurating granuloma, 2½ inches in diameter, somewhat resembling a sarcoma, was excised from the gluteus muscle.

Intravenous injections of quinine.—In pernicious cases of subtertian

malaria in which it is of importance to obtain a rapid and powerful action of the drug, the injection must be intravenous. The bihydrochloride salt of quinine should be used in a dosage of 10 gr., dissolved in 10 c.c. of distilled water. In algid or collapsed cases it may be advisable to add saline and glucose 5-per-cent. injection, in amounts of ½ to 1 pint, though in comatose cases it does not appear to be of any distinct advantage. The solution should be boiled in a test-tube before use, and drawn up in a sterile syringe and injected into the median basilic vein, rendered prominent by means of a rubber band. On its introduction into the vein the plunger of the syringe should be slightly withdrawn to observe the entrance of blood into the barrel. The injection should then be made slowly, and at least three minutes spent over the operation. One dose of 10 gr. is usually sufficient to stop the fever, and cause the disappearance of most of the parasites within eighteen hours, and it is advantageous to follow it up with an intravenous injection of 10 min. of adrenalin (1 : 1,000). The amount of toxin liberated by the rapid destruction of the parasites after intravenous injection may be sufficient completely to paralyse the cardiac mechanism, and death may rapidly ensue. It is much more advisable in cases where the myocardium is involved, to give a preliminary intramuscular injection of quinine, and to follow it up six or eight hours later by a small intravenous injection (6 gr.). After intravenous quinine a considerable fall in the blood-pressure is usually recorded. It is possible that more frequently repeated 3-gr. intravenous doses are more efficacious than are larger ones given at longer intervals. If great destruction of red blood-corpuscles has taken place, blood transfusion of 300–500 c.c. is strongly indicated.

The Ascoli treatment.—In Italy since this method was first introduced by Dominici in 1931 a good many papers have appeared on the subject. Ascoli's method consists in the intravenous injection of adrenalin 1/100, 1/90 and 1/80 mg. in increasing doses up to 1/10 mg. Usually about twenty injections are requisite. This method results in a reduction of the size of the spleen, in a decrease of the anæmia, in increase of body-weight and improvement in general health. It also increases the efficiency of subsequent quinine treatment, especially in those resistant to this drug (Pizzillo).

Milletari (1938) in 70 cases of malaria has confirmed the great value of this treatment. Its value lies, not only in its remarkable effect upon the splenomegaly, but also in the great improvement in the patient's general condition. He believes that it increases the patient's resistance to the malaria parasite, and this has been confirmed by D. Bell in Kenya.

II. Synthetic Anti-Malaria Preparations

Plasmoquine treatment.—Plasmoquine (6-methoxy-8-N (4′-diethylamino-1′-methylbutyl) aminoquinoline) is a compound produced by Schulemann, Schönhöfer and Wingler (1924), and is a derivative of methylene blue. When given to a man in a dosage of 0·06 grm. daily for five consecutive days, it has a remarkable specific action on the

[1] Bayer.

benign tertian and the quartan parasites, which disappear from the blood with a rapidity equal to that seen in the case of quinine; on the subtertian trophozoites the effect is not so satisfactory.

The therapeutic dose of plasmoquine is estimated by Mühlens as 1 mg. for each kg. of body-weight.

The rational therapeutic dosage of *plasmoquine simplex* is as follows:

0–6 months	0·0025 grm.
6 months to 2 years	0·005 ,,
2 – 4 years	0·0075 ,,
4 – 8 ,, ...	0·01 ,,
8 –10 ,, ...	0·015 ,,
10–15 ,, ...	0·02 ,,

The drug is dispensed in the form of tablets of 0·02 grm. each. The maximum dosage is 0·06 grm. daily.

In all four infections, the gametocytes are destroyed before the schizonts, so that the crescents of the subtertian parasite (which may persist for weeks in the circulation in quinine therapy) can no longer be found after four days' full dosage with plasmoquine. The spleen is also reduced in size with marked rapidity. Unfortunately, especially in heavy subtertian infections, a cyanosis, probably due to the conversion of hæmoglobin into methæmoglobin, is sometimes noted, and, in a few instances, has been followed by methæmoglobinuria (as in the fatal case reported by Blackie); abdominal pains are often produced, especially an acute spasm in the left hypochondrium, which may be connected with contraction of the spleen. De Langen and Storm have shown that both *plasmoquine* and *atebrin* in excessive doses cause circulatory disturbances, manifested in a reduction in the blood-pressure; and when injected *intravenously* (0·1 per cent. plasmoquine and 1 c.c. of a 2-per-cent. solution of atebrin) cause a fall of both systolic and diastolic pressures. In fatal cases acute hæmorrhagic nephritis and toxic necrosis of the liver occur.

Whether plasmoquine is liable to precipitate *blackwater fever* is still undecided and is difficult to determine on account of the tendency of this drug to produce toxic methæmoglobinuria. The test for determining plasmoquine in the blood and tissues is that of Nandi and Dickshit. Applied to the urine it is unsatisfactory. The test is sensitive in a strength of one in a million. The method is an application of Folin's phenol reagent, which is added to an aqueous solution of plasmoquine and rendered strongly alkaline by the addition of sodium bicarbonate. A blue colour develops, slowly reaching its maximum in thirty minutes, and can be detected in a dilution of 1 : 200,000 by the Duboscq colorimeter and of 1 : 1,000,000 by means of a spectro-photometer. The French preparation, Rodoquine (Fourneau 710), is therapeutically as active as plasmoquine, and is said to be less toxic.

Parenteral injections of plasmoquine.—Plasmoquine has been injected both intravenously and intramuscularly in 1-per-cent. watery solutions.

The dosage is graded according to age and physique and should not exceed 0·03 grm. twice daily for adults. On account of its toxic propensities, this course is not recommended.

Certuna, dialkylamino-oxyquinolamino-butane, has recently been reported by Kikuth as possessing a strong gametocidal action comparable with that of plasmoquine. The action upon the gametocytes and sporozoites is the same as that of plasmoquine, but its toxicity is less. Sioli has given 0·07 grm. three times daily for seven days with good results, and Mühlens reports upon 113 cases in which the drug was given in tablet form by the mouth and in severe cases by intramuscular injection of 0·3 grm. It can be given safely combined with atebrin. A similar drug has been synthesized by Schulemann under the name of "cilional." Missiroli and Mosna give 2 cg. daily for six days, but when used with quinine or atebrin it provides a complete antimalarial remedy, its action on the gametes of *P. falciparum* being equal to that of plasmoquine, and it is non-toxic in therapeutic doses.

Combinations of Quinine and Plasmoquine

Plasmoquine-compound.—The toxic effects of plasmoquine appear to be effectually counteracted by combining it with small quantities of quinine. The combination is now known as plasmoquine-compound and is put up in tablet form, each containing 0·01 grm. of plasmoquine and 0·125 grm. of quinine, which is twice the quantity contained in the tablet formerly manufactured. Plasmoquine-compound is comparatively tasteless. As far as has been at present ascertained, it is as effective in treating benign tertian malaria and in preventing relapses as is quinine. In the subtertian form the schizonts do not disappear from the blood with such rapidity as with quinine, but the same destructive action on the gametocytes is observed. Crescents disappear from the circulation after three days' full dosage.[1] This compound appears to be well tolerated by children. The following course of treatment with plasmoquine-compound can be carried out in all four forms of malaria. The exact amounts are stated in order to avoid confusion :

For an adult :

(1)	7 days.		2 tablets plasmoquine-compound twice daily.				
(2)	4 ,,	interval					
	7 ,,		2	,,	,,	,,	twice ,,
(3)	4 ,,	interval					
	7 ,,		2	,,	,,	,,	twice ,,
(4)	4 ,,	interval					
	7 ,,		2	,,	,,	,,	twice ,,
(5)	4 ,,	interval					

[1] The Editor has shown that subtertian crescents disintegrate and disappear from the circulation after 0.08 grm. (1⅓ gr.) plasmoquine and 1 grm. quinine. With pure quinine treatment, crescents may remain visible in the blood-stream for twenty-eight days and after 56 grm. of quinine.

(Plasmoquine-compound tablets as formerly manufactured contained each 0·005 grm. plasmoquine and 0·0625 grm. quinine. The maximum daily dose was 12 tablets.)

For pregnant women.—The scheme of dosage outlined above can be continued through the pregnancy and for several weeks subsequent to parturition.
For infants : 1 tablet plasmoquine-compound should be given daily.
[i.e. 0·01 grm. ($\frac{1}{6}$ gr.) plasmoquine + 0·125 grm. quinine.]
Children between 4 and 5 years : 1 tablet plasmoquine-compound twice daily.
Children between 5 and 10 years : 1 tablet plasmoquine-compound thrice daily.

Observations by the Editor go to show that the tendency to development of toxic symptoms may to some extent be eliminated by the exhibition of glucose, 1 fl. oz. daily, together with plasmoquine.

It has been shown by the Editor that plasmoquine-compound in therapeutic doses (0·04 grm. plasmoquine daily) is a safe drug to use in benign tertian, quartan and subtertian malaria, both during pregnancy and in the puerperium.

Quinoplasmine (Chinoplasmin). Plasmoquine : quinine 1 : 30.—This is a combination of plasmoquine with a much greater proportion of quinine than in the tablets of plasmoquine-compound. The tablet of quinoplasmine contains 0·01 grm. plasmoquine, 0·3 grm. ($4\frac{1}{2}$ gr.) quinine. The dose is three tablets daily for adults and represents a total dosage of $\frac{1}{2}$ grain of plasmoquine and 15 grains of quinine. Kligler, in Palestine, has used this preparation, given for five days in each month in the doses stated above, for reducing the parasite-rate in a malarious community : apparently no toxic symptoms were noted.

For practical purposes this is much the same method and dosage as was tested out by Manifold in India in 1930 when 3,187 British and Indian soldiers were given a three weeks' course of plasmoquine and quinine—plasmoquine 0·02 grm. (gr. $\frac{1}{3}$) together with 10 gr. of quinine every morning and evening. In the case of subtertian malaria the course was followed by 0·04 grm. plasmoquine daily for five days, but the majority were benign tertian infections. It was concluded that this course was most efficacious in preventing relapses, and was an advance on ordinary quinine treatment. It is possible, however, that in 0·1 per cent. of cases an attack of blackwater may have been precipitated.

III. Atebrin Treatment

Atebrin (quinacrine, French : acriquine, Russian) (dihydrochloride of 2-methoxy-6-chloro-9 (4'-diethylamino-1'-methylbutyl) aminoacridine)[1] is a yellow powder which dissolves in water at 40° C in 7-per-cent. solution. This dye was synthesized by Mietzch and Mauss in 1930.

Kikuth has shown that atebrin exerts specific action on the schizonts of all the malaria parasites, but it has no direct action upon the gametocytes, especially the subtertian. It attacks the ring forms first, then the developmental forms and, finally, if the atebrin is given

[1] A compound of this constitution is now being manufactured by Imperial Chemical Industries, London.

for a period sufficiently long, the gametocytes disappear ; but, as has been shown by the Editor and Walters, their power of exflagellation is not at any time affected, as it is with minute doses of plasmoquine. Undoubtedly its most striking effects are seen in the treatment of heavy infections of subtertian malaria. There is also some evidence that it is the safest drug to exhibit when blackwater fever is threatened, for atebrin does not possess the hæmolytic propensities of quinine.

A further advantage which this drug possesses over other malarial remedies is its comparative freedom from toxic symptoms, but these effects have been noted in some people with an idiosyncrasy, and in them it causes acute abdominal pain, sometimes so severe as to suggest gastric ulcer. Sometimes it produces a yellow discoloration, or staining, of the skin, which may be mistaken for jaundice. Atebrin pigmentation never occurs before the third day, while constipation and intercurrent infections modify the intensity and duration of the pigmentation ; sometimes it may last as long as three months. Recently the tablets have been coated with lacquer, which appears to have obviated this drawback, so that atebrin staining is no longer frequently met with. In differentiation from true jaundice, alcholuric jaundice and pernicious anæmia, it should be remembered that the scleræ are not affected by atebrin. Carotinæmia is easily distinguished.

Attention has recently been drawn to the fact that, in some, atebrin in large doses acts as a cerebral excitant, and the Editor has seen a few patients who have experienced feelings of undue excitement while taking atebrin. Conoley, Green and Hoops have noted the phenomenon in Malays, and Neave Kingsbury has reported some twelve cases of psychosis in Tamils, Malays, Chinese and Sinhalese after taking this drug. Some exhibited mild or transient psychoses, while others presented more serious symptoms necessitating special mental care. As an explanation of this effect, Kingsbury has suggested that the intense liberation of malarial toxins due to rapid destruction of the malaria parasites has an effect upon the cortical centres.

Blackwater fever may ensue after a course of atebrin, and this has now been noted by several observers. The Editor has seen one striking case of this ; but the general impression prevails that it is of less frequent occurrence than after quinine.

Atebrin is put up in tablets each containing 0·1 grm., and it is given three times a day *on a full stomach*. The daily dose therefore is 0·3 grm. ($4\frac{1}{2}$ gr.). Until recently it was considered that a five-day course of treatment sufficed to cure an ordinary case of subtertian malaria, but it is now realized that seven days may be necessary, during which a total of 2 grm. of the drug is given. The Editor considers that it is much safer to repeat the course, for a similar length of time, after an interval of a week. It is important that the tablets should be swallowed whole with a drink of milk or water, as the taste, when

they are chewed, is intensely bitter. Atebrin treatment is less satisfactory in benign tertian and quartan than in subtertian cases, and the reports on it from the tropics are, on the whole, favourable.

Atebrin treatment can be with advantage combined with 5–10 gr. of quinine hydrochloride daily. This method, which has been employed by the Editor, has been confirmed by Ciuca and his colleagues (1938) especially in severe subtertian infections.

In atebrin-treated malaria shrinkage of the spleen takes place as rapidly as in quinine- or plasmoquine-treated cases.

The drug is well borne in relatively large doses by children, and also by pregnant women, and these are important aspects of the subject. The most valuable property of atebrin is its power to prevent relapses, which it possesses in a high degree. Green, in 1932, treated 21 cases without relapses, while in a similar period there were 13 relapses among 34 controls treated with quinine. James and Nicol treated 15 cases of therapeutic (subtertian) malaria with 0·3 grm. daily for five days, and in only one did it fail to effect a permanent cure; and four of these were chronic relapsing cases which had previously been given several courses of quinine treatment. Hoops has reported that in Singapore atebrin treatment has given very satisfactory results both among Europeans and Asiatics; a sense of well-being is experienced after treatment with this drug which is not noted with quinine or plasmoquine. The relapse rate, over a period of six months, in 803 cases made up of approximately equal numbers of benign tertian and subtertian infections, has been reduced with atebrin treatment to 8·4 per cent. On the long course of quinine treatment it was 23 per cent., and with combined quinine and plasmoquine 20 per cent.

Atebrin is probably equal in therapeutic action to quinine, but it is slower in action, especially in subtertian malaria: it influences the fever, and gradually destroys the parasites. Nausea and headache disappear. Children tolerate atebrin well and the following doses are recommended:

Up to 1 year	0·05 grm. (i.e., half a tablet)
From 1–4 years	0·1 ,,
,, 5–8 ,, ...	0·2 ,,
Over 8 ,, ...	0·3 ,,

To children atebrin is best given in milk, or the tablet can be conveniently hidden in raisins.

Intramuscular injections of atebrin are less painful than those of quinine. Two injections with an interval of twenty-four hours are recommended. The drug in a soluble form (*atebrin musonate*) is supplied in sealed ampoules containing either 0.1 or 0.3 grm., and the contents are dissolved in 3 or 9 c.c. of water respectively. In very severe subtertian infections, however, its action is not so certain as intramuscular quinine and, in the Editor's experience, it should not be relied upon in these very severe cases.

With this strength (0·3 grm. in 9 c.c.) the dose is:

From 6 months to 2 years	1 c.c.
,, 2– 4 years	2 c.c.
,, 4– 6 ,,	3 c.c.
,, 6–10 ,,	4 c.c.
,, 10–12 ,,	5 c.c.
,, 12–15 ,,	6 c.c.
,, 15–18 ,,	7 c.c.

Field and Niven and Guest, comparing the action of atebrin musonate (intramuscularly and intravenously) in doses of 0·3 grm. on two successive days, found that parasites disappear from the blood and temperatures fall to normal as quickly as with quinine. The contents of each ampoule should be dissolved in 3 c.c. of water for intramuscular injection and in 9 c.c. for intravenous but, though the effects may be rapid, the cure is not permanent. Usually the local effects of intramuscular injection are transient, but in the Editor's experience large sterile abscesses have resulted. This method contra-indicated in cases with severe *anæmia*.

The excretion of atebrin is rapid. Traces have been found in the urine within ten minutes. Excretion usually takes place via the urine, to which it imparts a bright yellow colour, and the fæces. At the commencement excretion may be rapid; though it may be prolonged for several weeks, the average period being 26 days.

According to Hecht, atebrin is absorbed in the duodenum and taken to the liver, whence it is excreted in the bile. It therefore passes back again into the duodenum and, according to this theory, little atebrin reaches the circulation till the liver has been saturated. This may explain the fact that little atebrin appears in the urine until the treatment has been continued for some days. Peter has obtained laboratory evidence that food containing large quantities of cellulose absorbs atebrin from the intestinal canal.

Intravenous injections of 0/2 grm. atebrin musonate have been given in cerebral malaria, but quinine is preferable.

The *simultaneous* exhibition of atebrin and plasmoquine is *not to be recommended*, as it may cause alarming symptoms. On the other hand, an atebrin course followed by plasmoquine-compound is a rational procedure and has received wide commendation. The following method of application is recommended:

> Seven days' atebrin treatment followed by the administration three times daily, for three to five days, of 0·01 grm. plasmoquine simplex, or one tablet of quinoplasmine three times daily.

For children the after-treatment varies:

Infants, 0·005 grm. plasmoquine.
1–5 years, 0·01 grm. plasmoquine.
5–10 years, 0·01–0·02 grm. plasmoquine.

It has been observed that the malaria parasites undergo certain degenerative changes after the exhibition of both atebin and plasmoquine. The former causes an aggregation of the pigment of the parasite within two hours: the latter appears to act directly on the chromatin.

Reports on the success of this combined treatment come mostly from Malaya. In Central America Connor reported that relapses were 2–5 per cent. as against 25–30 per cent. after quinine treatment. In India the results in the British Army (1933–5) have been very favourable.

The method of estimation of atebrin in the blood and tissues has been the subject of some controversy.

The method of Gentzkow (1938) has been found accurate to 0·1 mgm. per litre. To 45 c.c. of acetone are added 5 c.c. of oxalated blood and the mixture is constantly shaken for a few minutes, after which 2 c.c. of a 20-per-cent. aqueous solution of neutral lead acetate are added. The whole is thoroughly mixed, transferred to a 50-c.c. centrifuge tube and centrifuged at a high speed for five minutes. The precipitated proteins are separated from the clear supernatant liquid to which is now added 5 c.c. of water. The mixture is evaporated to 2 c.c. on a water-bath, cooled, and added to 0·5 c.c. of 30-per-cent. phosphoric acid, and made up to the 5 c.c. mark with water. It is then filtered through No. 42 Whatman filter-paper. Of this filtrate, 4 c.c. are transferred to a small test-tube, and for each c.c. 0·1 c.c. of modified Tanret's reagent is added. The mixture is heated on a boiling water-bath for five minutes and cooled. A fine precipitate, which remains suspended for a considerable time, results. (For methods of estimating atebrin in the urine, *see* Appendix, p. 1029.)

Sulphanilamide (proseptasine) in the treatment of malaria.—Both sulphonamide and sulphanyl-sulphanilate have been found effective in ape-malaria, *P. knowlesi*, especially by intraperitoneal injection. The effect of these compounds upon the human infections has been the subject of much study. Motzfeldt, in a review of recent work, thinks that all three principal forms of malaria appear to be amenable to treatment with sulphanilamide, but whether the effects are permanent or not is not clear. Hill and Goodwin have now reported upon the treatment of 100 cases with *prontosil soluble*, 7 of which were due to *P. vivax* and 93 to *P. falciparum*. In most, prontosil was injected intramuscularly, 10 c.c. every twelve hours, and it was seldom found necessary to give more than four injections.

Treatment of simple benign tertian or quartan attacks.—During a paroxysm of ordinary intermittent fever it is better, before giving quinine, to wait until the rigor and hot stages are over and the patient is beginning to perspire. When the skin is moist and the temperature begins to fall, the earlier the drug is commenced the better: 10 gr., preferably in solution, should be administered at the commencement of sweating, and thereafter 10 gr. three times a day after meals for the next three days, though there appears to be an advantage in giving it, whenever possible, in smaller doses at more frequent intervals—6 doses of 5 gr. each. If the patient is constipated, a saline purge should be administered before the quinine is exhibited. This is an almost certain cure. The quinine may not always prevent the next succeeding fit, but it nearly always diminishes its severity; in ninety-nine cases out of a hundred the second following attack does

not develop. At the same time, with a view to preventing recurrence of fever, the patient is directed to take, once a week, a mild saline, sulphate of soda or Carlsbad salts, in the morning, and three 5-gr. doses of quinine during the day, or 15 gr. in one dose. After the first week, iron and arsenic are given, in pill or tabloid, such as :

Ferri hypophos. . . .	gr.ii	(0·13 grm.)
Quin. sulph.	gr.i	(0·065 grm.)
Acid. arsen.	gr. $\frac{1}{50}$	(0·0013 grm.)
Strych. sulph. . . .	gr. $\frac{1}{50}$	(0·0013 grm.)

Two pills to be taken at night for a fortnight.

The antirelapse treatment with plasmoquine-compound may be then given by those who prefer this method.

Treatment of subtertian malaria.—Mild cases of malaria of the subtertian type, due to *P. falciparum*, may be treated on the same lines as the benign forms, with quinine and especially with atebrin (*see* p. 119).

Rest is a most important factor. It is undoubtedly true that the malignancy of many cases of subtertian malaria observed in military service is due, to a great extent, to the exigencies of war.

The sooner after infection a case of subtertian malaria is treated by quinine or atebrin, the more rapid the recovery and the less likelihood there is of relapse or of the development of pernicious symptoms.

In the endemic area of blackwater fever, and in persons who have left the area, large doses of quinine do sometimes undoubtedly determine an explosion of that dangerous disease, especially in the cachectic.

Treatment of cerebral malaria.—In a threatened cerebral attack ice-bags should be applied to the head at the same time as hot applications to the feet and legs ; inhalations of oxygen are advisable ; artificial feeding may be necessary. In order to obviate the accumulation of parasites in the brain it has been recommended that the patient should be made to inhale amyl nitrite in order to make the parasites more accessible to quinine ; and in order to bring the quinine solution into intimate contact with the parasites, adrenalin—10 minims of 1 : 1000 solution—may be injected intravenously.

In the case of coma or convulsions, one should also take into account the fact that a considerable œdema of the brain and increase of cerebro-spinal fluid have been demonstrated in fatal cases in which no sporulating parasites could be found in the cerebral capillaries. In comatose cases which do not clear up after intravenous injections of quinine (15 gr.), lumbar puncture and withdrawal of 20 c.c. or so of cerebro-spinal fluid may give great relief. Cordes has actually recommended, and performed, puncture of the cisterna magna at the base of the brain, 50–60 c.c. of fluid being allowed to escape. The effect of decompression is striking and immediate. As a general rule, increasing coma after intravenous quinine, especially if accompanied by signs of cerebral irritation, is due to multiple punctate

subcortical hæmorrhages. Sayers, in the Solomon Islands, and G. Thomson in Nyasaland, have emphasized the great value of lumbar puncture, especially in convulsions in children.

Thomas and Sydenstricker treat cerebral malaria by giving 2–4 litres of Ringer's solution subcutaneously during the first twenty-four hours to combat dehydration. Dextrose solution, 10 per cent., is given intravenously—500 c.c. every four to six hours. Quinine dihydrochloride, 0·5 grm., is added to the first dextrose injection and repeated every six hours till cerebral symptoms disappear.

Umansky has advocated intravenous injections of urotropine—3 c.c. of a 40-per-cent. solution; it does not affect the malaria parasite but it is claimed that its effects upon the cerebral functions are good.

Atebrin can be given intravenously as *atebrin musonate,* in doses of 0·1 to 0·2 grm.

Treatment of bilious remittent fever.—In bilious remittent and other severe forms of malarial fever one must not wait for the remission before giving quinine. To wait for remission or sweating used to be the practice; it was said that to give quinine at any other time was wrong, and that something terrible would happen if the superstition were ignored. *In all grave fevers a full dose,* 10 *or* 20 *gr., should be administered at once.* The parasite cannot be attacked too soon. It is desirable to have the bowels freely opened with salts as quinine undoubtedly acts better then, especially when given intramuscularly.

For vomiting and other severe symptoms, fragments of ice may be sucked, small doses of morphia injected, or counter-irritation applied to the epigastrium.

Treatment of hyperpyrexia.—Hyperpyrexia must be promptly met by prolonged immersion in the cold bath, rectal injections of iced water, ice-bags to the head, etc. At the same time quinine must be injected intramuscularly. Prompt action in these cases is of the first importance, and may save life. If the temperature be kept down for three or four hours the quinine gets time to act on the parasites crowding the capillary vessels; but if the temperature be allowed to mount and to remain high the patient is destroyed before the specific has a chance. The cold bath, therefore, is absolutely necessary. In such circumstances, antipyrin and similar antipyretics are worse than useless. A good rule is to prepare to give the cold bath or cold pack if the axillary temperature reaches 106° F., and to remove from the bath when the rectal temperature has fallen to 102° F.

Treatment by salvarsan and its derivatives.—These drugs appear to have some influence upon *P. vivax* (benign tertian), but they seem to have no effect upon the subtertian or the quartan parasite. When given in therapeutic doses in the apyretic periods they do not seem to prevent ordinary relapses. Many practitioners, however, are in the habit of employing weekly injections of salvarsan as an adjuvant to quinine treatment, and there is little doubt that in some cases it acts as a general tonic and improves the physical condition of the patient; but it is in those cases—unfortunately not exceptional

—in which syphilis as well as malaria is present that their action is most marked.

Stovarsol (*see* p. 542) in 4-gr. tablets, dosage one to two tablets daily for ten days, has been claimed to have a curative effect in benign tertian malaria. It is doubtful, however, whether this is the case, though the drug possesses a marked tonic and stimulating action. Such large doses, 15 gr. daily, as advocated by French writers, are certainly to be avoided, as toxic erythema and other disagreeable sequelæ are liable to ensue. According to some authorities, quinine and stovarsol act better in combination than when given singly (quiniostovarsol).

Mapharsen (meta-amino-parahydroxy phenylarsine oxide), a potent trivalent arsenical, which has been used for the treatment of trypanosomiasis, has been employed intravenously for cutting short malarial attacks. Goldman recommends that the patient be kept fasting and the drug given intravenously in doses of 0·04 to 0·06 grm. according to the body-weight. In 90 per cent. of cases a single injection suffices to end a malarial attack, but if it does not do so the injection may be repeated within seven days. This drug is said to be of special value in treating severe cases of therapeutic malaria. The disappearance of parasites is almost immediate.

Treatment of malaria-infected patients on return from the tropics.—If quinine is being taken when the patient leaves the tropics for Europe, *its use, in the accustomed dose, should be systematically continued during the voyage and for a month or more after arrival.*

The importance of this practice cannot be too strongly stressed, especially when returning in the winter months. It has become a routine—and it is a very wise one—to administer a prophylactic course of *atebrin* for five to seven days to all those returning on board ship from West Africa.

TREATMENT OF BLACKWATER FEVER

Having regard to the frequency with which hæmoglobinuria concurs with malarial infection, and the well-established fact that *quinine* may precipitate or determine a hæmoglobinuric attack, the question of the administration of that drug in blackwater fever becomes important.

Recommendations.—Patients who are suffering from or are threatened with hæmoglobinuria, who are in the *pre-blackwater state* (p. 91), or who have had this disease before, on the slightest indication of fever should go to bed at once, keep the skin warm and scrupulously protected from draughts, and take plenty of warm fluid; if parasites are present in the blood, the patient should be treated with full doses of atebrin and an alkaline mixture; if this drug is not available, small doses of quinine, commencing with 1 gr. twice daily, should be given, together with a moderate dose of calomel. Patients threatened with blackwater fever should not travel; should it become imperative for any reason to move the patient, a small injection of morphia should be given, or he may be kept under slight chloroform

anæsthesia[1] during the worst part of the journey. Some believe that, by giving large doses of aperient sulphates (1 oz.) every four hours to patients in this state, and thus by the profuse catharsis relieving the hepatic congestion, the onset of blackwater fever may be averted. The principles of treatment should be based upon the appreciation of the underlying pathology of the condition, namely the extensive hæmolysis, coupled with the precipitation of the insoluble acid hæmatin in the urinary tubules, the plugging with cellular debris, and their consequent damage and disorganization. Glucose in large quantities by mouth and intravenously in 5-per-cent. solution is indicated, as it has been shown by Kubo and Kondo that this sugar possesses the property of preventing hæmolysis of the red corpuscles by quinine.

As clinical evidence and certain experimental work indicate that suppression of urine is much less likely to occur if the urine remains alkaline, massive doses of sodium citrate, either alone or together with sodium bicarbonate, should be given until the urine is alkaline. It may be necessary to give as much as 1 drachm at four-hourly intervals until this is produced. If the symptoms be more severe, intravenous injections of sodium bicarbonate, 150 gr. to 1 pint of distilled water, should be administered without delay (Hanschell). It is not advisable to inject more than one pint at a time, and it should be given slowly, on account of the danger of œdema of the lungs.

If the urine still tends to be suppressed, *caffeine citrate*, 2 gr. twice in the twenty-four hours, should be given as a bland diuretic. In these circumstances hot fomentations should be applied to the loins, or cupping by Fenwick's glasses should be instituted, plenty of bland diluents administered, and an exclusive milk diet ordered until the albumin has disappeared from the urine. High rectal lavages with hot water have a marked diuretic effect, while Ross, in Southern Rhodesia, advocated lavage of the pelvis of the kidneys by means of ureteric catheters. After introduction of the catheters—a skilled proceeding—a syringe containing 4 c.c. of warm sterile saline is attached and the fluid injected and again withdrawn about twelve times. In the mildest as well as the gravest cases, the free and frequent administration of fluid is a most important measure, whether the patient is thirsty or not, and should be insisted on from the beginning of the attack. When owing to persistent vomiting, it cannot be retained by the stomach, rectal enemata of warm physiological *salt solution* (much less irritating to the bowel, and thus far more likely to be retained than plain water) should be administered repeatedly, 6–8 oz. every half-hour or hour, and in some instances Murphy's drip saline method *per rectum* is to be recommended. Turpentine stupes, mustard plasters and hot fomentations to the epigastrium are useful in controlling or ameliorating the vomiting; when severe, the time-honoured resort to sips of iced champagne is useful and agreeable. If these are not effectual,

[1] Burkitt in Kenya recommended intramuscular injection of sodium luminal, which kept patients quiet for two days.

salt solution (a teaspoonful to the pint of water), sterilized, may be slowly introduced into the subcutaneous connective tissue of the flank or elsewhere by means of a hollow needle attached by a rubber tube to some improvised reservoir placed one or two feet above the level of the patient. The water is rapidly absorbed, and cannot fail to be useful in washing out the hæmoglobin infarcts which plug the renal tubules and bring about, or at all events contribute to, suppression of urine. In cases with convulsions or coma. 5-per-cent. *glucose solution* given intravenously to the extent of two or three pints is advocated. Marked restlessness may require minute doses of *morphia* ($\frac{1}{60}$ gr.); but the drug, of great use at times, must be employed with caution. For the very severe anæmia which results, *liquor arsenicalis* (2 min.) may be administered four-hourly. Antipyretic drugs, as antipyrin and phenacetin, are dangerous.

Transfusion of compatible blood has been successfully practised in the Hospital for Tropical Diseases, and should be adopted in severe cases from the moment that the hæmolysis commences. It has been shown abundantly that this is a natural procedure calculated to replace the red blood-corpuscles which have been destroyed. Considerable care must be exercised in grouping the blood, as the cells in these severe hæmolytic states are prone to auto-agglutination. Repeated transfusion can be employed, as much as 300–500 c.c. being given on each occasion. There is no evidence as yet to show that it arrests the process of hæmolysis. With the replacement of active functioning red blood-cells the urinary excretion is rapidly re-established and the proportion of blood-urea falls once more to its normal level. In the field in Southern Rhodesia, Blackie has stressed the great practical importance of this procedure. He considers it a life-saving measure and emphasizes that transfusions must be repeated until there is hæmatological evidence of active erythropoïesis.

Nursing is a most important element in the management of blackwater fever. If the stomach will retain food, this should be given in a bland and fluid form, but there should be no attempt at forcible feeding, especially with rich and indigestible viands. One precaution against syncope must be sedulously enforced: the patient must not be allowed to sit up, much less to get out of bed, until food has been retained and assimilated, and the risk of sudden death has passed. The foot of the bed should be raised on blocks. During convalescence iron therapy, which is easily tolerated, such as *hæmatinic plastules* (Wyeth), may be given three times daily. Injections of liver extract are also indicated; Otto and Naumann find that injections of crude liver extract (*campolon*) in large doses considerably assist blood-regeneration, and furthermore that this substance exerts a specific action upon the liver.

Usually a severe attack of blackwater fever wipes out the associated malaria infection; but this is not always so, and a relapse of fever with parasites in the blood is by no means an uncommon

occurrence. In order to guard against this contingency, an after-course of atebrin treatment is always advisable.

If possible, the subject of blackwater fever should quit the endemic area, and never return to it or to any malarial locality ; a severe attack, or a second attack, implying as it would special liability, should be regarded as an imperative indication to this effect.

Prophylaxis of Malaria and Blackwater Fever

The basis of malaria prophylaxis is the fact that particular species of mosquitoes are necessary for the propagation of the parasites. Complete extermination of mosquitoes, or even of all anophelines, by antilarval measures has been found to be impossible. It is much more practical to concentrate on particular species which are known to be efficient carriers of the disease.

Anti-mosquito measures. In order that anti-mosquito measures may be effectively carried out, it is necessary that a preliminary survey should be made of the malarious districts in order to formulate a plan of anopheline breeding-places. A study of such a survey plan enables the sanitarian to decide definitely upon the localities from which the malaria arises.

In order to prevent mosquito breeding in *streams* and *waterways*, it is necessary to get as even and swift a flow as possible without eddies or back-waters. The stream should be canalized, that is to say, the sides should be sloped at an angle of 45 degrees. Embankments should be lined with large stones and the vegetation cleared from the edges. An occurrence specially to be guarded against during the monsoon is the formation of pools after the subsidence of extra high flood. A stream thus treated is practically self-sterilizing except when we are dealing with a species of anopheline like *A. maculatus* which is specially adapted for life in rocky streams. Springs of water amongst rocks also afford suitable breeding-places to the last-named species. Whenever possible canalization should be supplemented by oiling. Subsoil drainage can be employed in place of canalization and, indeed, forms an important feature of estate sanitation in the Federated Malay States.

Seepage, or infiltration of water through bunds or dykes at the bottom of a hill foot, usually forms a fruitful breeding-ground for anophelines. These seepages are especially met with in " paddy " or rice fields. *Running swamps* in the course of a stream in level country form dangerous breeding-spots. They can be dealt with if the vegetation is first removed, when oiling becomes possible. *Borrow pits*, formed usually in the process of railway construction, may, when several years old, form suitable breeding-places. When recently excavated the water is too muddy for anopheline larvæ to thrive, and when the borrow pits contain larvivorous fish they are usually innocuous and in this contingency should not be treated with cresol. *Tanks*, in India and Ceylon, are seldom dangerous, but, if the margins are much overgrown with vegetation, certain anophelines may obtain a foothold. When these tanks are used for washing clothes (dhobying), the soap and other chemical substances employed are fatal to mosquito larvæ.

Rice fields are dangerous when the water is kept in continuous motion through the fields ; uncultivated plots in terraced fields that are allowed to become flooded are especially so. In Java the drying-off of the fields throughout a tract on one day each week has been made obligatory and is efficacious

without apparently damaging the growth of the rice. To the inexperienced eye there might seem enormous potentialities for breeding anophelines in paddy fields, but the rice fields themselves are not always to blame as much as the irrigation ditches. *Standing swamps* are not dangerous when they contain a large population of predaceous insects and fish which prevent much anopheline breeding. In America these undrainable swamps have been rendered less dangerous by dusting with Paris green from an aeroplane.

Mangrove swamps, especially in the Andaman Islands, are associated with virulent malaria due to the breeding of certain species of anophelines, especially *A. ludlowi*, in saline water. Sunlight also is necessary for the development of these larvæ. Thus the dense virgin mangrove forest is healthy so long as it is daily traversed by tides ; but when trees are cut down, or when bunds are constructed to interfere with tidal movements, and derelict pools are formed which are gradually diluted by rainfall to a suitable salinity, the breeding of anophelines takes place. Drainage is difficult at sea-level unless there is a big tidal range. In Malaya, owing to the sixteen-foot drop in the tides, it has become possible to install automatic sluice-gates to the bunds.

Smaller collections of water which, if overlooked, may constitute a grave danger by breeding the dangerous species of anophelines, will next be considered. A sagging gutter may hold enough water to support large numbers of larvæ ; moreover, a good deal of atmospheric moisture is condensed upon the roofs of tropical bungalows so that the gutters are constantly being replenished even in the absence of rain. It is probably better to remove eave gutters entirely and allow the water to drip into shallow cement drains placed suitably round the bungalow. Holes in rotten trees may breed a limited number of anophelines; indeed one European species, *A. plumbeus*, breeds exclusively in this situation. *Wells* are a certain source of trouble where they are built within native houses and where, in the absence of light, species of anophelines have adapted themselves. In Palestine and Macedonia they have been found to be the main breeding-place of *A. bifurcatus*, one of the chief vectors of malaria in these regions. In Bombay City the house wells are inhabited by *A. stephensi*.

Anti-mosquito rules generally adopted are as follows :

Surface drains.—These should be as narrow as possible in proportion to the amount of water they have to carry. The sides of the drain should be sloped at an angle of 60 degrees ; less steeply in friable soils ; grass growing at the bottom of the drain should be pulled out by hand. Lateral drains into the same channel should be alternated so as not to bring in one from each side at the same spot. In some places, as in Trinidad, it has been found more effective to blast tracks of drains by means of dynamite.

Subsoil drains consist of unglazed collarless pipes buried beneath the floor of the drain sufficient to carry the normal flow from springs and seepages. Unless these pipes are actually functioning for several months of the year, the cost of their installation is not justifiable. They are especially adaptable to ravines, as in the plantations in the Federated Malay States. There it is found advantageous if they are overgrown by a grass covering which prevents silting and over-flowing.

Oil.—Oiling kills mosquito larvæ probably in several ways, but mainly by suffocation and its toxic action. Green has shown that the rapidity with which larvæ die depends upon the volatility and toxicity of the oil. Crude liquid petroleum is preferable to kerosene oil. Its

spreading power can be improved by the addition of 1–2½ per cent. of castor or coco-nut oil. In Palestine Kligler found the most effective mixture to be 1 part of crude oil to 4 parts of kerosene, with the addition of 0·1–0·2 per cent. castor oil. *Anti-malarial oil* (A.M.M.) is a mixture containing diesel oil, solar oil and kerosene put up by the Asiatic Petroleum Co. *Pesterine* is another mixture of oils, prepared by the Burmah Shell Oil Co. *Liquid paraffin* has been used by Swellengrebel and others in Holland. An almost colourless oil, it costs about £1 per cwt., and it is claimed that its effects are not vitiated by wind or rain, that it does not evaporate, and that it does not prevent mosquitoes from ovi-positing.

Murray lays down the following conditions for anti-larval oils as far as film stability is concerned :

(1) The oil should contain either a small aromatic content or a very high one.

(2) It should not contain 50 per cent. aromatics, unless they are very high-boiling (e.g., of lubricating base fraction). It should consist of a mixture of wide and overlapping cuts of oil.

(3) It should not contain fats, or fatty acids, added as spread-aiders. If the presence of these is desired, resins should be employed.

The oil may be applied to the water in several ways. Spraying consists of forcing the oil under pressure through an atomizing nozzle from a special machine. Of the various patterns the " Kent " sprayer best suits the capacities of the tropical labourer. Sprayers should be fitted with leather or flexible metal adjustments, as petroleum oil perishes rubber in a few days. For road-side ditches oil carts may be used, but for all purposes the knapsack sprayer is the most adaptable. The best oil for the purpose is a heavy oil which will issue from the sprayer as a fine cloud and spread uniformly over the water. Oil swabs, or cotton-wool steeped in oil and weighted down by a stone, when thrown into water are ideal for rock springs and running streams. Balls or " guddas " may be made of tow or sacking weighted with stones, and, after being soaked in heavy oil, are thrown into pools. The oil gradually oozes out and comes to the surface. A " gudda " is shaped like an ordinary pillow and is 28 in. long by 16 in. broad. It is made of sacking and will soak about two gallons of oil and last about three months. Local buffaloes may be made use of by oiling them by night, so that when they " wallow " the next day they act as animate " oil bombs." In certain malarial districts in the United States oil-soaked sawdust has been found to give a more complete and permanent oiled surface. The material has the advantage of being easily transported. The oil gradually exudes and spreads as an even film over the surface of the water, entering the spiracles and breathing-tubes of the larvæ and suffocating them. In Panama drip cans and barrels are used from which the oil constantly drips from cork wicks or through holes from which nails project. Their value as an oiling

agent is less than that of sprays. Oil must be applied at *seven-day intervals;* any deviation from this rule will afford a generation of anopheline larvæ ample opportunity to hatch out. If properly treated, the vegetation at the margins of the stream or pond should be burned down for a foot on each side, and water-plants such as *Spirogyra* should disappear.

Cresol is the basis of the many disinfectants on the market, and should be present in any compound in a strength of 15 per cent. Being capable of killing larvæ in a dilution of 1 : 40,000 within three hours, it forms an excellent larvicide, but it kills off all other forms of life at the same time. Fish killed in this manner are distinctly poisonous if eaten. Cresol *is very useful* in *ponds and standing* water when oil cannot penetrate or is blown away by prevailing winds. In Panama the following preparation is used: 200 lb. of finely-crushed resin are thoroughly mixed with 15 gallons of crude carbolic acid: 30 lb. of caustic soda dissolved in 6 gallons of water are added. This mixture, which is highly poisonous to larvæ in a dilution of 1 : 10,000, forms an emulsion when added to fresh water. It may also be used as a diluent for heavy oil.

Paris green, an expensive compound, is copper aceto-arsenite and, in the quantities used for anti-mosquito work, is said to be harmless to other forms of life; the particles are eaten by the anopheline larvæ and act as a direct poison; culicine larvæ are not affected in the same manner as the surface-feeding anophelines; fish are not killed. The powder should be intimately mixed with one hundred times its weight of finely-sifted dry road-dust, or soapstone, and sown by hand, down wind, over the water at the rate of 170 gr. of Paris green per ten square feet of water surface. The length of time the particles remain afloat depends upon the surface tension and the more plentiful the vegetation the greater this is. In America (western Tennessee and northern Alabama), dusting machines have been invented for this purpose, and in large marshes the services of aeroplanes have been called into use. The dilution obtained for this purpose is 1 : 3, speed 60 miles an hour at a height of 25–200 ft. It is believed that one plane can cover 20 square miles a day with this substance.

Anopheles quadrimaculatus is the species most easily controlled by thi method. The aeroplane designed for the purpose is a Stearman, model 4-D, open biplane with a 300 h.p. motor. The special equipment consists of a plywood hopper of 21 cubic feet capacity installed in front of the pilot's cockpit, so as to place the dust load as near the centre of gravity as possible. The cost of operating a dusting aeroplane works out at $40 per hour. Thirty-three acres per minute can be treated for $0.367 per acre, but perfect dusting weather conditions do not always occur. Aeroplane dusting for anopheles control on impounded waters is practical, effective and economic. In India, Brasier-Creagh advocates the D.H. 83 Fox Moth as the most suitable machine, with structural modification, including a hopper and a Ventura tube. The pilot should wear a canvas suit and gas helmet. The cost works out at two to three shillings per acre.

Greenglide, a preparation made by Craven & Co., Evesham, has an advantage over crude Paris green in so far that it will float for weeks. Its composition is:

Arsenious oxide	55·37
Copper oxide	31·12
Water-soluble arsenic	1·00

Great success has attended this method in the Pontine marshes and in Sardinia. The frequency with which Paris-greening should be undertaken varies in different localities and depends upon the rate of development of the larvæ.

Copper sulphate is especially useful in tanks where water is stored for drinking purposes and where sheets of algæ are sheltering larvæ. Its action is not direct upon the larvæ themselves, but is one of starvation by killing off their food supply.

Stoxal, of Messrs. Poulenc, is a special preparation of formalin, or paraform, and is regarded by Roubaud as being most destructive to anopheline larvæ, while at the same time harmless to fish, and in this respect superior to Paris green and other arsenical powders. It is an extremely light powder of great buoyancy, and yet so fine and impalpable that its particles can be ingested by the smallest larvæ. Being so light it can be dispersed over great distances by the wind. One centigramme of the powder suffices to kill all anopheline larvæ over one square metre of surface. The surface of the water must be agitated so that the powder sinks and forms a suspension. For ordinary use it is mingled with fifty times its volume of dry sand and the mixture is then distributed by hand or shovel. On reaching the water the stoxal dissociates from the sand-grain and forms a film fatal to anopheline larvæ.

Oil-burning of marshes.—Waste oil is employed. A mixture of light shale and heavy fuel oil has been found best. The marsh is well oiled and the oil then ignited by means of oil-soaked waste. Once the fire has started, and is spreading, it is fed by sprays of light oil ejected from garden syringes. When the heavy oil catches fire it burns for hours over vegetation and shallow stretches of water. Great numbers of adult mosquitoes can thus be destroyed, and shallow larvæ-containing pools dried up; even, in the case of deeper water-stretches, the larval stages are to some extent eliminated.

The Hay flame-gun or flame projector, manufactured by Messrs. Hubbard Bros. Ltd., Basingstoke, Hants, weighs between 50 and 60 lb. and is a cylindrical steel container filled with a mixture of inflammable oil. The machine will project a continuous jet of liquid fire to a distance of 80–90 ft., lasting for half a minute.

The prevention of mosquito breeding in uncovered and unscreened wells has peculiar difficulties. Oiling water with petroleum is apt to mar its taste. Williamson has recommended the liberation of gases and vapours for this purpose in wells. Paraformal (3 oz. per square

yard) vaporized at the bottom of a three-foot shaft will kill anopheline larvæ in half an hour. Sulphur dioxide acts by acidifying the water. When using gases, wells should be closed, and for this purpose a portable parachute to be lowered into the well has been devised.

Mosquito-netting.—It is very necessary that the mosquito-netting used should be of reliable quality and should keep out all mosquitoes. In order to do so it should contain as many as 25 or 26 holes to the square inch[1] (Fig. 12). The best varieties are known as "bobbin" netting, and should be woven of 30's cotton; by this

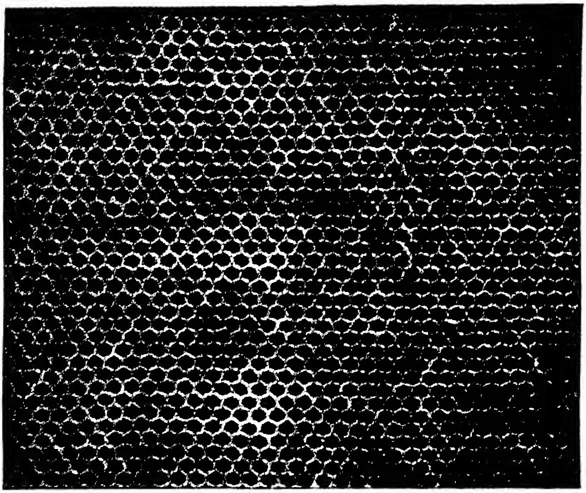


Fig. 12. Mosquito-netting, 25/26 holes to the sq. inch.
(*MacArthur, Jl. R.A.M.C.*)

is meant that 1 lb. of the thread will reach 30 times round a circumference of 840 yards.

The nets must be used invariably. They should be tucked up underneath the mattress before retiring to bed. Some prefer to allow the net to hang down so as to reach the floor, but if this be done, care should be taken to see that it is in contact at all points, since otherwise the insects may crawl in underneath. During the daytime the net should be rolled up and placed behind the head of the bed, and all necessary precautions should be taken to see that it contains no mosquitoes before being arranged for the night, otherwise it becomes a mosquito "trap" and not a protection. Light attracts mosquitoes, therefore the cautious tropical resident will see that he is adequately protected by his mosquito-netting before going

[1] It is necessary to explain that the square inch of the net trade is not that of the mathematician; it means that the count is made along two lines of holes which fall within an opening one inch square (Fig. 13). Thus it does not mean that there are actually 25 holes to the square inch—in fact the more exact number would be about 150.

to rest in a brightly illuminated room. For the same reason the blinds are best kept down while preparing for the night, to be drawn up again immediately the light is put out.

When travelling by train in a malarious country, difficulty is often experienced in suspending a net in a railway compartment. Small hooks attached to rubber discs which will adhere by suction to any smooth surface will be found most useful for this purpose.

The body should be covered up during sleep, and every precaution (e.g. fires) that circumstances permit should be employed to keep mosquitoes away.

The subjects of malarial infection are dangerous to their companions; they should therefore be avoided, or, if this is impracticable, compelled to sleep under efficient mosquito-nets. *Mosquito boots* of soft leather or canvas or Wellington boots—protect the ankles and legs in the evening; for ladies, a pillow-case drawn up over the legs and feet is a useful precaution. Joss-sticks may be burned *under* the table to deter mosquitoes. The Japanese pattern—"kathol coil"—is recommended. *Veils and gloves* are used to protect soldiers and others on night duty.

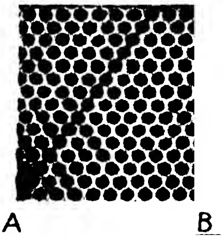


Fig. 13.—Shows the correct method of counting the mesh of cotton netting. The mesh of this net is the sum of the counts made along the lines A B and A C, the hole at A being counted twice. (*MacArthur, Jl. R.A.M.C.*)

Mosquito repellents. *Fumigation.* Chinks in doors and windows should be closed; one window only should be left uncovered, and a white sheet should be placed on the floor in front of it. The mosquitoes, being stupified by fumigation, will fall on the sheet and then can easily be seen, swept up and burnt. Mosquitoes may be driven out of railway carriages, ships, or barges by careful fumigation. For this purpose various substances have been recommended, of which pyrethrum powder is probably the most effective. Pyrethrum powder (*Pyrethri flores*) is made from the dried flower-heads of the pyrethrum. It forms the chief ingredient of many insect powders, such as Keating's. The powder may be used dry and puffed into the air of the room. For fumigation, it is heaped up in an iron pot into a little pyramid, which when lighted burns slowly, giving off a dense and pungent smoke. One pound is necessary for 1,000 cubic feet of space, and the room should be kept closed for three hours.[1]

Sulphur dioxide, when used in the Clayton apparatus, and the vapours derived from cresol or hydrocyanic gas are also employed.

Flit, a proprietary preparation, has many advocates, but is expensive to use on a large scale.

Many other proprietary sprays are on the market, most of them having

[1] For further details the reader is referred to "Malaria Control by Anti-mosquito Measures," by Gordon Covell. Thacker, Spink & Co.

a basis of kerosene oil. The following may be mentioned: Flytox, Mosquil, Shell-tox, Whiz, Flyosan, Fly-ded, Necrosene, Rids, Alio Spree and Abis.

The cost of these preparations is so high that most sanitarians use a locally-prepared mixture, such as that of Brug and Van Slooten (a mixture of kerosene with 2 per cent. of *carbon tetrachloride*) known as "rids." The mosquitoes, stupefied by the spray, are burned immediately afterwards, but sprays of this nature must not be used in the vicinity of naked lights. There is usually a very considerable movement of anopheles in and out of buildings, so that spraying must be repeated at frequent intervals (3–4 days). The formula of several sprays is as follows:

(1) Giemsa's spray:

Pyrethrum tincture	580 parts
Potash soap	180 ,,
Glycerin	240 ,,

Diluted with 20 volumes of water before use: 100 grammes of the fluid suffice for 50 cubic metres of space.

(2) Lefroy's spray:

Pyrethrum	2 lb.
Alcohol	1 gall.
Saprol	1 gall.
Soap	*q.s.* to

form an emulsion; usually about 10 ounces. In hot climates add ½–2 per cent. of castor oil.

Dilute 1 in 30 before use.

(3) Army fly spray:

Pyrethrum powder	117 parts
Spirit. rect.	912 ,,
Camphor oil	780 ,,
Powdered hard soap	2·37 parts

For personal use many oils and ointments have been advocated; they are smeared on the hands and face. The proprietary preparation known as Sketofax is recommended by many. Bamber oil has a big reputation; this consists of oil of citronella 1½ parts, kerosene 1 part, coco-nut oil 2 parts, made up with 1 per cent. carbolic acid as a preservative. Cod-liver oil rubbed on hands and face is highly recommended.

As oil of citronella, used as a mosquito-repellent, often irritates the skin, the following formula (Army official anti-mosquito cream) has been found to be effective:

Oil of citronella	18.25 per cent.
Camphor	1.0 ,, ,,
Cedar-wood oil	9.0 ,, ,,
Paraffinum durum	26.25 ,, ,,
Paraffinum molle (white)	45.0 ,, ,,

The paraffin should be melted and other constituents then added. The mixture being well stirred, it should be bottled and cooled rapidly, preferably by placing the bottle in a basin of cold water. It is also useful for sandflies.

The following mixture has the additional advantage of reducing insect bites, but is very irritating to the skin, especially that of the face, when used as a repellent when the weather is very hot:

Ol. cinnamomi	ʒii	(7·1 c.c.)
Ol. cajuputi	ʒi	(3·55 c.c.)
Formalin (40-per-cent. formaldehyde) . .	ʒi	(3·55 c.c.)
Alcohol (90-per-cent.) ad	℥iv	(28·42 c.c.)

The irritation of a bite may also be allayed by rubbing the puncture with a moist cake of soap, or by applying 1-per-cent. alcoholic solution of menthol, or a 1 : 20 carbolic solution. Hydrogen peroxide or weak ammonia solution is also useful.

A dilute solution of magnesium sulphate, 1 ounce to 10 ounces of water, applied to the skin is said to act as a preventative against mosquito-bites; it has the advantage of being cheap and not irritating. The juice of a fresh-cut lime fruit rubbed well into the skin and allowed to dry is an excellent preventative.

These measures are undoubtedly of some value, but they are tedious and sometimes disagreeable to apply, and must only be looked upon as adjuvants to other measures to protect from mosquito-bites.

Direct chemoprophylaxis.—At present doubts are being expressed upon the value of quinine as a true prophylactic in malaria. Stott's experiments with native Indian troops, of which one-half (over 3,000) received prophylactic quinine (quinine gr. 15 three times weekly for five months) while the other half did not receive any, showed approximately equal admission rates to hospital for malaria. Celli's well-known figures for relative value of prophylactic measures were as follows:

Mosquito protection and quinine prophylaxis	1·76	per cent.	infected
Mosquito protection alone	2·5	,,	,,
Quinine prophylaxis alone	20	,,	,,
No protection at all	33	,,	,,

The experience of the Great War was, on the whole, to discredit its prophylactic value. The practical outcome is that quinine prophylaxis is inapplicable to scattered bodies of men under inadequate medical supervision.

Yorke and Macfie have shown that under experimental conditions the sporozoites injected by an infected mosquito are not destroyed or harmed even when the patients are taking 30 gr. of quinine daily; that is to say, the therapeutic dose of quinine does not prevent the onset of a malarial attack; in other words, against the sporozoite, quinine is apparently ineffective. Quinine has no direct action upon the plasmodia in the trophozoite stage, as was shown by Mühlens and Kirschbaum, who mixed a quantity of malaria blood with a solution of quinine, 1 : 10,000, leaving the mixture for twelve hours, but yet were able to infect a patient by direct inoculation and, still more, were able to show that *A. maculipennis* may still be infected by feeding on a malaria subject who is taking quinine.

Whatever may be thought of quinine prophylaxis as an army measure, there can be no doubt that most residents in tropical countries lay great store by it, and it is among the European officials and settlers on the Congo and in East Africa that a systematic quinine prophylaxis

is most appreciated. It is therefore, for the present, advisable to give 5 gr. of quinine hydrochloride in liquid form, every night, or 15 gr. twice weekly, or on a week-end system for two consecutive days (Koch) towards evening in highly malarious countries, but probably in the near future our ideas regarding its practical application will have to undergo modification. If it is not a parasitic prophylactic, nearly every one is agreed upon the value of *regular* quinine prophylaxis in mitigating the clinical phenomena of malaria and in preventing the onset of blackwater fever.

Plasmoquine chemoprophylaxis.—In England more than fifty experimental trials have been made on this subject. In all the tests it was proved that the infecting mosquitoes were really *infective* by dissection of the salivary glands and by using untreated patients as controls. The amount of plasmoquine necessary to prevent infection has varied between 0·06 and 0·08 grm. daily, and this must be given at least three days before and at least five days subsequent to the infecting bite. With smaller doses of plasmoquine, which are naturally much more easily tolerated, there have been many more failures than successes; but, apparently, the incubation period of the malaria attack is postponed for a considerable period (in benign tertian from three to six months). In a few of the apparent successes with smaller doses there was an "abortive attack" within the usual incubation period, followed some months later by a true attack (recrudescence). It is probably true, at present, to state that true chemoprophylaxis of malaria can be attained, but only with such doses of plasmoquine as are perilously near the toxic limit, doses which cannot possibly be tolerated by residents in tropical malarious countries. Although Henderson (1934) in the Sudan has succeeded in reducing the morbidity from malaria in a population by two-thirds by means of a daily dose of 0·2 grm. plasmoquine, there is insufficient evidence to show that it is of greater value than atebrin or quinine.

Mosna has found that quinoplasmine, 0·02 grm. given twice weekly to adults and proportionately less to children, during five months in a hyperendemic area, resulted in marked reduction of morbidity in the general population and a marked reduction of incidence among small children and babies.

Atebrin chemoprophylaxis.—The idea has been expressed that possibly atebrin could act as a malaria prophylactic on account of its property of being stored or retained in the body. Atebrin has been exhibited in 0·3-grm. doses over a period of 5–7 days, and does not prevent penetration of the sporozoites into the tissues but possibly acts upon them when they have entered the blood-stream. James and Shute have performed experiments with atebrin similar to those with plasmoquine and have succeeded in delaying the attack of malaria for as long as thirty-three to thirty-seven weeks after mosquito infection.

For prophylactic purposes 0·1 grm. of atebrin appear to be more effective than 0·3 grm. of quinine.

Weekly doses of 0·4 grm. are sufficient to maintain health. A daily dose of 0·05 grm. of atebrin (half a tablet), on account of its slow excretion, is not advisable.

The requisite dose is 0·4 grm. weekly, preferably in one dose of 0·2 grm. on Wednesdays, and a second similar dose on Saturdays.

Children may be given :

Up to 2 years, 0·05 grm. (half a tablet).
2–4 years, 0·075 grm. (three-quarters of a tablet).
5–8 years, 0·1 grm.
Over 8 years, 0·2 grm.

The doses are given with two clear days' interval after each. Hoops writes enthusiastically of this method in suppressing the clinical manifestations of malaria in a labour force in Malaya.

CHAPTER IV

HUMAN TRYPANOSOMIASIS

Definition.—Morbid conditions produced by parasites belonging to the genus *Trypanosoma*, including irregular and chronic fever, skin eruptions, local œdema, adenitis, physical and mental lethargy and, in a large proportion of cases, death. The trypanosome is spread by the tsetse flies (*Glossina*) in Africa, and by winged bugs (*Reduviidæ*) in Central America.

The trypanosomes are blood parasites which are widely distributed in animals, especially in big game, in the countries in which these diseases occur. These animal hosts act as reservoirs of the trypanosomes which cause disease in man. The geographical distribution of human trypanosomiasis is shown in Map I; that of the African forms in Map II.

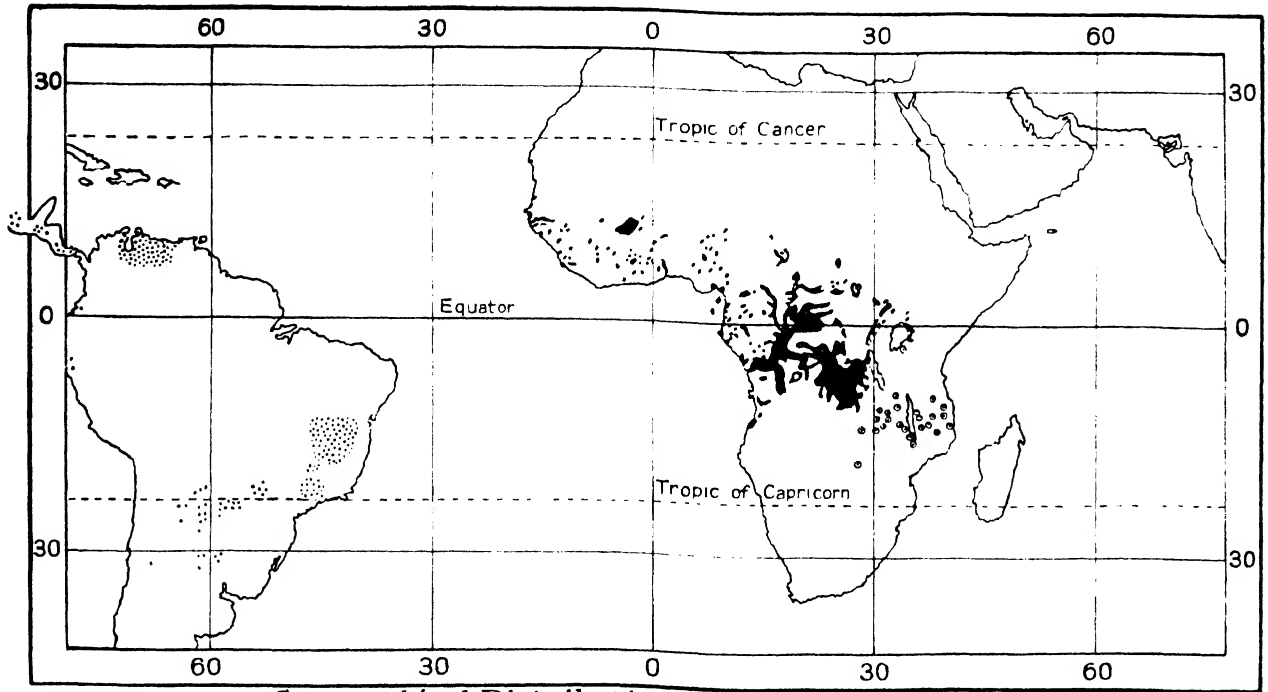
I. AFRICAN HUMAN TRYPANOSOMIASIS

History.—Human trypanosomiasis, or sleeping-sickness, has been known for well over a century, but it was not till some thirty-eight years ago that the pathogenic cause was definitely recognized. In 1901 Forde encountered a trypanosome in the blood of a European suffering from fever in Gambia. In 1902 Dutton found a similar organism in the blood of a native of that colony, and suggested the name of *Trypanosoma gambiense* to designate the parasite. In the next year Castellani found the trypanosomes in the cerebrospinal fluid as well as in the blood of sleeping-sickness cases in Uganda; and his suggestion that the parasite is the cause of the disease was fully confirmed by Bruce, Nabarro, and others. (Fig. 14.)

Gambiense Sleeping-Sickness

Geographical distribution (Map II).—The distribution of this disease corresponds roughly with that of the tsetse fly, *Glossina palpalis*. It is found in scattered areas on the Gambia, in Sierra Leone, the Gold Coast, Nigeria, the Cameroons, the Southern Sudan, and Uganda; but its main stronghold is along the waters of the Congo and its branches. In the Sudan an endemic focus existed in the Bahr-el-Ghazal Province, but has greatly diminished in extent, though *Glossina palpalis* is found in a belt, 1,000 miles long, ranging towards Darfur. The most southerly focus in Africa has been found in the Okavango and Chobe swamps in Ngamiland, on the borders of the South African Union.

Ætiology.—Neither age, sex, occupation, nor race *per se* has

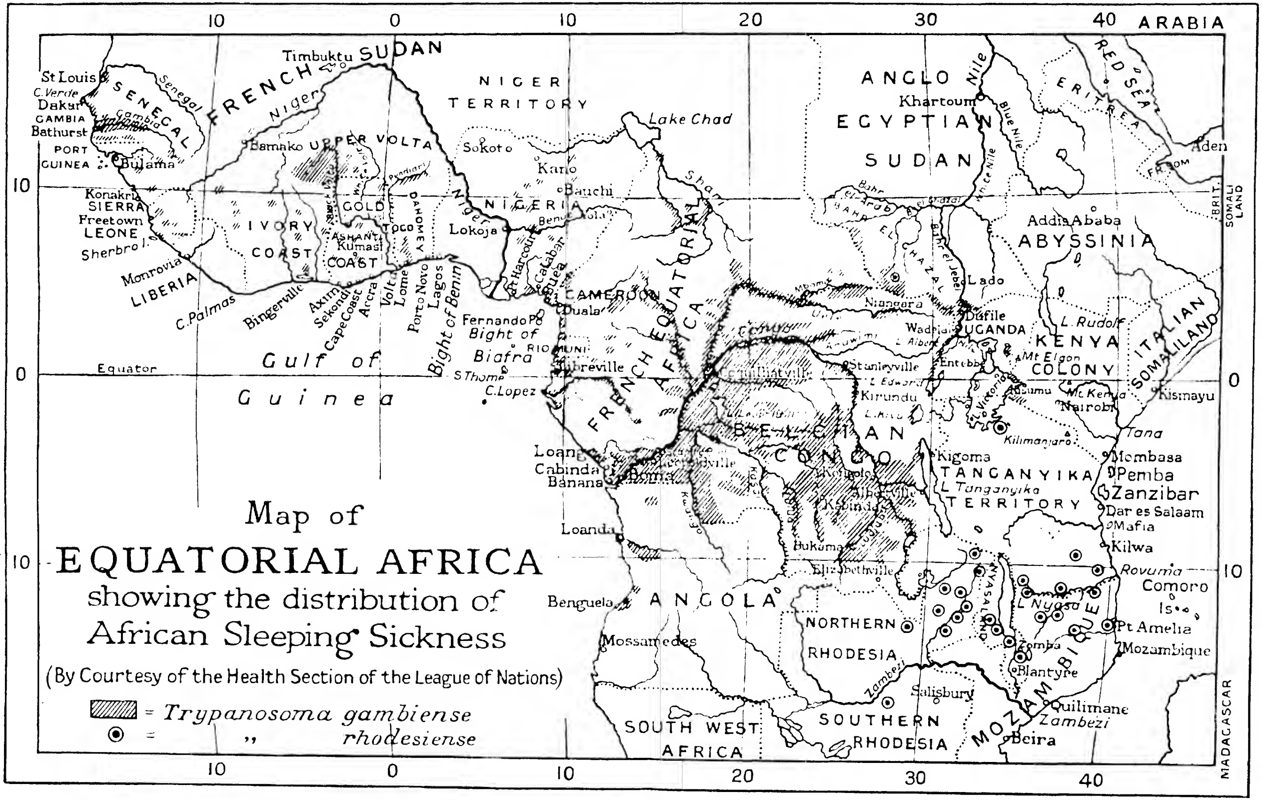


Amended May 1939

Geographical Distribution of Trypanosomiasis

■ = *T. gambiense* ⚬⚬ = *T. rhodesiense* ⁘ = *T. cruzi in man*

MAP I


Map of
EQUATORIAL AFRICA
showing the distribution of
African Sleeping Sickness
(By Courtesy of the Health Section of the League of Nations)
= Trypanosoma gambiense
= ,, rhodesiense
ARABIA
RED SEA
ERITREA
Aden
ANGLO EGYPTIAN SUDAN
Khartoum
Nile
Blue Nile
ABYSSINIA
Addis Ababa
ITALIAN SOMALILAND
BRIT. SOMALI LAND
Kismayu
KENYA COLONY
L. Rudolf
Mt Elgon
Mt Kenya
Nairobi
Tana
Mombasa
Pemba
Zanzibar
Dar es Salaam
Mafia
Kilwa
Rovuma
Comoro Is.
Pt Amelia
Mozambique
MOZAMBIQUE
Quilimane
Zambezi
Beira
MADAGASCAR
TANGANYIKA TERRITORY
Kigoma
L. Tanganyika
Kilimanjaro
UGANDA
Entebbe
Dufile
Lado
Wadelai
L. Albert
Bahr el Jebel
BAHR EL CHAZAL
Bahr el Arab
Niangara
Stanleyville
L. Edward
Kirundu
BELGIAN CONGO
Kabinda
Bukama
Elizabethville
NYASALAND
L. Nyasa
Zomba
Blantyre
NORTHERN RHODESIA
SOUTHERN RHODESIA
Salisbury
Zambezi
SOUTH WEST AFRICA
ANGOLA
Loanda
Benguela
Mossamedes
Loango
Cabinda
Banana
Boma
FRENCH EQUATORIAL AFRICA
Libreville
RIO MUNI
CAMEROON
Duala
Buea
Calabar
Pt Harcourt
Fernando Po
Bight of Biafra
S Thome
C. Lopez
Lake Chad
Shari
NIGERIA
Kano
Bauchi
Sokoto
Lokoja
Niger
Benue
NIGER TERRITORY
SUDAN
FRENCH
Timbuktu
Bamako
UPPER VOLTA
DAHOMEY
TOGO
GOLD COAST
ASHANTI
Kumasi
Volta
Lome
Porto Novo
Lagos
Bight of Benin
Accra
Cape Coast
Sekondi
Axim
IVORY COAST
Bingerville
C. Palmas
LIBERIA
Monrovia
Sherbro I.
SIERRA LEONE
Freetown
Konakri
PORT GUINEA
Bulama
Bathurst
GAMBIA
Gambia
Dakar
C. Verde
St Louis
SENEGAL
Senegal
Gulf of Guinea
Equator
10
0
10
20
30
40
Cribb & Co.

MAP II

any influence on the susceptibility to trypanosome infection, except in so far as those factors conduce to opportunity. Thus, Schwetz has found a baby of twenty days old infected in the Belgian Congo. Occupations (boatmen, fishermen, water-carriers) which entail frequenting of the waterside haunts of the glossina conduce to infection. In common with other trypanosomes, *T. gambiense* (Fig. 14), as seen in fresh blood, is an active, wriggling organism, having a spindle-shaped body which is slightly compressed laterally and spirally twisted. Dividing forms are sometimes met with.

There is no uniformity in the number of parasites present in the blood: sometimes they are fairly abundant, one or two in each field

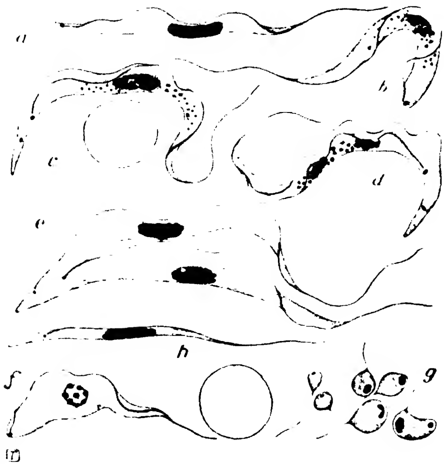


Fig. 14.—*Trypanosoma gambiense*: **various forms from blood and cerebro-spinal fluid.**

a, Elongated posterior extremity; *b*, blunt ditto; *c*, *d*, and *e*, dividing forms; *f* and *h*, probably sexual forms, *g*, small round forms from cerebro-spinal fluid.

of the microscope; at other times, and in the same patient, it may be difficult or impossible, even after prolonged search, to find a single specimen; in some instances they tend to recur cyclically at intervals of a week or more. On the whole, although this is by no means invariably the case, the parasites are most abundant in the blood during the febrile attacks to which the hosts are so subject. The blood appears to be not their only or principal habitat. They are usually found with ease in the enlarged lymphatic glands, and also occur in the cerebro-spinal fluid, as well as in that of the serous cavities. They have been found also in the substance of the solid organs, including the brain, where they are distributed throughout the tissues outside the blood-vessels.

The parasite may be cultured on N.N.N. medium (*see* p. 1039). It can usually be inoculated into most mammals, including all the ordinary domestic

and laboratory animals, and is especially pathogenic for the rat, but considerable variations in virulence are encountered. Monkeys, especially *Cercopithecus patas*, and dogs are susceptible, while amphibia and reptiles are immune. Inoculation of susceptible animals may be used for demonstrating the presence of the parasite when they occur in very scanty numbers in the peripheral blood, and is sometimes successful in those rare cases where they cannot be found after careful microscopical examination.

As shown by Laveran and others, these trypanosomes undergo agglomeration, both in blood and in artificial cultures, when exposed to unfavourable biological conditions.

How long a trypanosome infection may persist in the human body has not been definitely determined, but there is direct evidence that it may continue for many years. From what we know of the incubation period of sleeping-sickness, it is not improbable that this period is sometimes greatly exceeded, and may extend to seven years or longer.

Transmission.—This trypanosome is not usually transmitted hereditarily in human beings, although the organisms have been found in the placental blood of infected rats, as well as in the livers of their embryos. As in kala-azar, intrauterine congenital transmission occasionally has been noted, and in Germany there is a record of one case having occurred in a European (Mühlens).

Darré and his colleagues recognize the frequency of hereditary trypanosomiasis in the French Congo and have demonstrated trypanosomes in the cerebro-spinal fluid of a child born of an infected mother.

Rôle of the tsetse fly as transmitting agent.—There is no evidence that biting flies other than the tsetse are concerned in the spread of human trypanosomiasis, but there are apparently two ways in which this fly is able to transmit the trypanosome: (1) cyclical, and (2) mechanical.

(1) *Cyclical transmission.*—As originally demonstrated by F. K. Kleine in 1909, *T. gambiense* undergoes an endogenous cycle of development in the circulating blood of the vertebrate. Certain short forms are regarded as the adult or metacyclic type, and they alone are responsible for carrying on the exogenous cycle. When taken up into the fly (Fig. 15) the trypanosomes first multiply in the mid-gut, and, if the contents of the intestine at this stage are injected into the susceptible animal, they do not convey the infection. After an elaborate development, lasting 12–20 days, the infective forms of trypanosomes become congregated in the salivary glands. (For further details, *see* p. 873.)

There is no doubt now that transmission ordinarily occurs through the bite of infected flies, the trypanosomes passing through the salivary duct in a similar manner to the sporozoites of the malaria parasite. The adaptation of *T. gambiense* to *G. palpalis* is remarkably specific, for the parasite normally develops in this fly (Plate V). In Western Nigeria and in certain districts of the Gold Coast, however, *Glossina tachinoides* has been found infected in nature and is mainly responsible for epidemics of sleeping-sickness in those countries. There is no evidence that the tsetse fly can transmit the trypanosome to its offspring.

Van Hoof, Henrard and Peel have found that the index of cyclical transmissibility of trypanosomiasis on the Congo can be calculated by the formula—

$$I = \frac{g}{1} \times \frac{n \times 100}{N} \quad \text{where—}$$

I = index of cyclical transmissibility, i.e., the number of glossina which after the fifteenth day were found to harbour trypanosomes ;

n = the total number of glossina found during the whole experiment ; and

N = number of glossina dissected during the experiment.

The mean index of transmissibility for the Congo is 3·63 ; the index of infectivity is 6·17, and the metacyclic index is 0·61 per cent.

(2) *Mechanical transmission.*—Duke, in Uganda, has suggested, on epidemiological grounds, that mechanical transmission by the glossina of a virulent strain of *T. gambiense* from man to man may be responsible for some epidemics.

Reservoir-hosts. — In the plateau province, Northern Nigeria, Taylor finds that, in the absence of game and suitable aquatic reptiles, which form the normal buffers, the fly feeds for the most part on man. The question of shade, which is only to be found in the vicinity of native villages, is also to be considered. The combination of these factors has conduced to an extraordinary degree

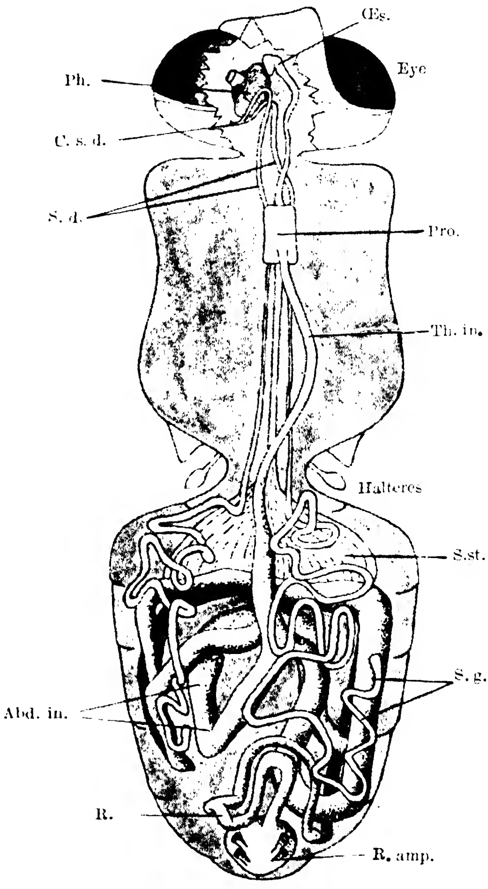


Fig. 15. General view of digestive tract of *Glossina palpalis.* (*After Minchin, "Report on Sleeping-Sickness to the Royal Society."*)

Ph., pharynx ; Œs., œsophagus ; C. s. d., common salivary duct ; S. d., salivary ducts ; Pro., proventriculus ; Th. in., thoracic intestine ; S. st., sucking stomach ; S. g., salivary glands ; Abd. in., abdominal intestine ; R., rectum ; R. amp., rectal ampulla.

of contact between the tsetse and man. The rate of trypanosome infection of the fly is correspondingly high. There are other areas, in Uganda, where the same condition has been noted. Considerable attention has been drawn to the wild game which act as reservoirs of the infection. It has been proved that eleven common kinds of antelope (bushbuck, reedbuck, and waterbuck) can be inoculated with *T. gambiense* by feeding upon them experimentally-infected tsetse flies; furthermore, it has been established that certain of the marsh-haunting antelopes, especially the situtunga—Speke's antelope (*Limnotragus spekei*)—are quite commonly infected under natural conditions with *T. gambiense*, and Duke found that antelopes of this species persisted in an infected state in the islands of Victoria Nyanza four and a half years after the population had been removed by Government orders as an attempt to check the spread of sleeping-sickness.

Speke's antelope (*Limnotragus spekei*) is a handsome animal standing 36 in. high at the withers, the buck possessing fine spirally-twisted horns. In ground-colour it is of a uniform greyish-brown, but the head is adorned with white ocular and cheek spots and a white chin. A very wary creature, living in dense and impenetrable papyrus, it is seldom seen or shot by Europeans. The hoofs of this antelope are long and widely splayed, an admirable adaptation to its habitat, but when living on dry land they become shorter and modified accordingly.

The domestic stock must be now considered to constitute a reservoir of infection for man, since *T. gambiense* has been found by various observers in oxen, goats, and sheep in Tanganyika Territory and East Africa. Van Hoof states that in the Belgian Congo the domestic pig forms an ideal reservoir host, and he found infected specimens of these animals which had been reared in Leopoldville. In the pig the trypanosome does not produce the slightest pathological effects.

Pathology.—The chief lesions are found in the lymphatic glands and in the central nervous system; there is general enlargement, with congestion and, it may be, hæmorrhage of the lymphatic glands, especially those of the triangles of the neck and submaxillary region and the mesentery.

No gross lesions of the nerve-centres, or of any other organ, have been described as invariably present; but in every case indications, principally microscopical, of an extensive meningo-encephalitis can be demonstrated. In a proportion of instances congestion of the meninges, effusion of lymph, and increase and turbidity of cerebro-spinal fluid, are found. In all cases, as first pointed out by Mott, there is an extensive small-cell infiltration of the perivascular lymphatic tissue throughout the brain, cord, and meninges,[1] varying in amount in different cases and in different anatomical regions (Fig. 16). The invading cells are glia cells, lymphocytes, and morular cells (Mott);

[1] Known in Germany and on the Continent as "Dürck's nodes."

the latter are fuchsinophile hyaline cells, analogous to those found in granulomata, and can be demonstrated in sections of the cortex. They are probably degenerated plasma cells, as the nucleus stains deeply and is often displaced. The cytoplasm consists of a number of clear spherules, giving the cell a mulberry appearance; they correspond to the "*Körnchen-Zellen*" of Alzheimer and are possibly of the same structure as Russell's bodies. Thus the essential pathological feature of sleeping-sickness recalls the very similar condition in general

Fig. 16.– Section of brain in sleeping-sickness, showing round-cell infiltration filling perivascular space. (*Orig. case, Dr. A. C. Stevenson, "Trans. Roy Soc. Trop. Med. and Hyg."*)

paralysis of the insane, and also in disseminated sclerosis. The lumina of the vessels are contracted, and their walls are thickened. The cells of the spinal cord usually show fewer changes than those of the medulla and the cerebral cortex. Experimental work by Yorke, Wolbach and Stevenson has shown that the lesions of the lymphatic and nervous tissue are due to actual invasion of the solid organs by the trypanosomes, for they have been seen in the brain tissue, mainly in the frontal lobe, pons, and medulla, where they can be demonstrated in masses or nests (Fig. 17), with no definite relation to the blood-vessels. Trypanosomes often occur in the cerebro-spinal fluid, which they enter from the choroidal plexus where, as Peruzzi has shown, they occur in masses in

active stage of division. There is said to be an increase in the lymphatic tissue of the lymph follicles and Peyer's patches of the small intestine. The spleen is usually moderately enlarged, and the trypanosomes have been demonstrated there in the pulp tissue.

Peruzzi, in his researches into the pathology of experimental trypanosomiasis in monkeys, has shown that myocarditis of a severe degree is frequently present, and that this is due to massed collections of trypanosomes in the muscle-cells.

Symptoms.—The *incubation period* of the glossina-conveyed disease and that resulting from direct artificial inoculation seem to be about

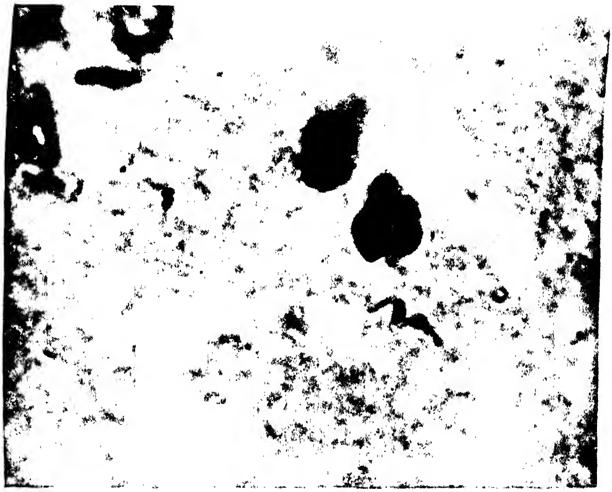


Fig. 17.—Photomicrograph of frontal lobe of brain in sleeping-sickness, showing trypanosomes in grey matter. (*Orig. case, Dr. A. C. Stevenson "Trans. Roy. Soc. Trop. Med. and Hyg."*)

the same, from two to three weeks, in the case of dogs, horses, and monkeys. From experiences of infected Europeans, in whom the ates can be controlled, it would appear to be usually about fourteen days. The bite of an infected glossina is followed, in a proportion of cases, by a degree of local irritation of greater or less severity. This has been called the "trypanosome chancre" and is described as a red nodule surrounded by a white waxen zone. It subsides in the course of a few days, to be followed, sooner or later, by fever, which may last a week or longer, and may be accompanied by the appearance, in Europeans at all events, of a peculiar type of erythema and a certain amount of serous infiltration of the connective tissue (Plate IX, Fig. 1). Apparently, the trypanosomes appear in the peripheral blood about twenty-one days after the infecting bite. A form of hyperæsthesia, known as "Kerandel's symptom," is usual, though not invariable, when

the patient strikes a limb against any hard object, a degree of discomfort amounting to actual pain is experienced, the sensation being slightly delayed. In time the fever subsides more or less completely, to recur at irregular intervals of days or weeks. The fever is sometimes mild, sometimes severe, and occasionally hyperpyrexial (106·6° F.), the evening temperature being always the highest. The fever may last for weeks; the apyretic period may be equally prolonged. On the other hand, the fever may be continuous. Irregularity of degree and duration is a feature of the fever, and also of the other clinical manifestations of trypanosomiasis. In time the patients become debilitated, anæmic, feeble both intellectually and physically. Severe headache is very often complained of. The heart's action is generally rapid and easily excited, and it has been pointed out that persistent tachycardia affords an excellent index to persistent infection. The cervical glands and the glands of other parts of the body enlarge and may become tender. It may be that only one gland is visibly involved, or there may be a recognizable general polyadenitis, including the abdominal glands. The implicated glands may be very prominent, or they may not be easily felt; they are usually most conspicuous in the posterior triangle of the neck (Winterbottom's sign) (Fig. 18). In the early stage of the infection they are soft, later indurated. Sometimes they are painless, sometimes distinctly painful and tender, rarely suppurating. This condition of irregular fever, of debility, of polyadenitis, of slight anæmia, may go on for months, or even, in some instances, for years.

A proportion of cases may terminate at this stage. Considering that the disease may present at various stages periods of quiescence, which in some instances may be very prolonged, it would be rash to say whether in any instance of apparent recovery we are dealing with a radical cure, or merely with one of these long periods of latency. But experiments and observations by Laveran and others in other forms of trypanosome infection, as well as cases of the disease in Europeans which have come under the Editor's notice, justify the belief that occasionally the parasite does die out spontaneously.

It would appear that in a given area and in a given population there is a tendency for the virulence of the local trypanosome to decrease with lapse of time. Thus, the trypanosome of the Gold Coast and Southern Nigeria, where sleeping-sickness presumably has long been endemic, is less virulent and much more amenable to treatment than that of Uganda, where it is of recent introduction; indeed the Editor, together with Cooke and Gregg, has described a series of particularly mild cases in Europeans from the Gold Coast in which the trypanosome was discovered during the course of routine blood examination, and in which neither glandular enlargement nor splenomegaly could be demonstrated. In one there was a characteristic circular erythema on the shoulder. Similar instances have been recorded by Lamborn, Howat, Davy, Sieé, Rolin and Mercier.

Remarkable features of human as well as of animal trypanosomiasis

are the skin affections and the local œdemas. In many of the lower animals affected with their special trypanosomes, in addition to fever and physical lethargy, papular and pustular eruptions are not uncommon; and in man, especially in negroes, an exceedi[illegible] papular eruption is a common symptom. In the F

Fig. 18.—Enlargement of cervical lymph-glands in trypanosomiasis (Winterbottom's sign). (*Dr. F. K. Kleine.*)

possibly in the negro—but in the latter, in consequence of his colour, not so evident—extensive skin areas are affected with a fugitive, patchy, frequently annular erythema (Plate IX), usually most evident on the chest and back, but also very often on the face, legs, and elsewhere. This erythema seems to occur most frequently and most distinctly in the earlier stages of the infection. Some of the patches may extend to six inches or even a foot in diameter, their margins

fading off insensibly into the surrounding normal skin. Sometimes it takes the form of large rings, occasionally complete, more frequently interrupted and irregular. Erythema nodosum sometimes occurs also. Pressure or any irritation of the skin gives rise at once to transient congestion from vasomotor paralysis of the skin capillaries. This rash can be brought out by heat, and especially by immersing the body in a hot bath.

In some of the lower animals a usual feature is œdema of certain parts of the body, especially the sheath of the penis, the under-surface of the abdomen, and the neck. Similar, though less extensive, œdemas occur in man, in whom they are most apparent in the face and about the site of the erythema. In many instances there is a general fullness of the features which, together with concomitant flushing of the face, is apt to convey a false impression of sound health.

Neuralgic pains, cramps, formication, and paræsthesiæ of different kinds are not uncommon. In two of Manson's European cases, recurring orchitis, accompanied by an increase of parasites in the blood, was a feature. Painful local inflammatory swellings, which after a time subside without suppuration, have been seen in three cases; periostitis of tibiæ once. A toxic irido-cyclitis and choroiditis and deep œdema of the lower eyelid are sometimes met with. The eye symptoms are not so evident in man as in the lower animals, keratitis in infected dogs being comparatively frequent.

In most cases the spleen is enlarged, sometimes enormously so, the swelling fluctuating with the fever. The liver also may be enlarged. As the patients affected with trypanosomiasis are usually the subjects of malarial disease, it is not always possible to say whether the splenic enlargement is entirely or partly attributable to the trypanosome.

Although, according to Greggio, trypanosome infection is not, as a rule, transmitted to the fœtus, the abortion-rate in the infected is increased from the normal 7 per cent. in Congo natives to 31·7 per cent., and the infant mortality-rate from 29 per cent. to 50 per cent. Trypanosomiasis in infants is extremely rare, though Kellersberger has recorded infection in one three weeks old (*see* p. 140).

Death from intercurrent disease, or from rapidly developing cerebral implication causing convulsions, the status epilepticus, coma, etc., may supervene at any stage of trypanosomiasis. Usually the case gradually drifts into the stage known as "sleeping-sickness." [1]

Sleeping-sickness stage.—The terminal stage of trypanosome infection sometimes exhibits acute features, sometimes it is exceedingly chronic. While in a proportion of instances an interval of several years, possibly seven, may elapse from the commencement of the infection to the development of this terminal stage, in the

[1] It is customary to state that the development of the sleeping-sickness stage in trypanasomiasis concurs with and is dependent on the entrance of the parasite into the cerebro-spinol canal.

majority of cases the march of events is much more rapid. The characteristic terminal symptoms depend on implication of the nervous system either by the parasite itself or by its toxins.

According to Low and Castellani, the average duration of this stage of trypanosomiasis in the African is from four to eight months, not infrequently less; very chronic cases with a course of more than a year's duration are rare. Other observers refer to cases running on for three years or even longer, and occasionally presenting temporary ameliorations.

Generally the first indications of the oncoming of sleeping-sickness are merely an accentuation of the debility and languor usually associated with trypanosome infection. There is a disinclination to exertion; a slow, shuffling gait; a morose, vacant expression; a relaxation of features; a hanging of the lower lip; a puffiness and drooping of the eyelids; a tendency to lapse into sleep or a condition simulating sleep, the somnolence during the day-time contrasting with restlessness at night; a slowness in answering questions; a shirking of the day's task. Dull headache is generally present. Later there may occur fibrillary twitching of muscles, especially of the tongue, and tremor of the hands, more rarely of the legs, indicating a definite involvement of the motor centres. By this time the patient has taken to bed, or he lies about in a corner of his hut, indifferent to everything going on around him, but still able to speak and take food if brought to him. He never spontaneously engages in conversation or even asks for food. As torpor deepens he forgets even to chew his food, falling asleep perhaps in the act of conveying it to his mouth, or with the half-masticated bolus still in his cheek. Nevertheless, such food as he can be got to take is digested and assimilated. Consequently, if he is properly nursed, at this stage there may be no general wasting. As time goes on he begins to lose flesh, tremor of hands and tongue becomes more marked, and convulsive or choreic movements may occur in the limbs or in limited muscular areas. (Fig. 19.) Sometimes these convulsions are followed by local temporary paralysis. Sometimes, too, rigidity of the cervical muscles and retraction of the head occur. There is usually an intolerable pruritus of the skin as originally observed by Manson in the first cases of the disease studied in England. Bedsores tend to form; the lips become swollen, and the saliva dribbles from the mouth. Gradually the lethargy deepens, the body wastes, the bedsores extend, the sphincters relax; and finally the patient dies comatose, or sinks from slowly advancing asthenia. Possibly he succumbs to convulsions, hyperpyrexia, pneumonia, dysentery or other intercurrent condition.

The manifestations described are subject to considerable variations. Thus, mania is not uncommon; delusions may present themselves, or psychical and physical symptoms not unlike those of general paralysis of the insane are developed. In the European,

death is frequently due to convulsions, probably from the presence of the trypanosomes in the brain. Deep hyperæsthesia of the muscles is also quite common. The habits are usually bestial.

During the whole course of the nervous stage of trypanosomiasis the other symptoms already described as characteristic of the infection may be in evidence. The knee-jerks, though lost towards the end, are active at first; the fundus oculi is normal; the sphincters, until towards the end, are controlled; the urine is normal, and the bowels, although generally tending to constipation, act with more or less regularity.

Complications.—In the Central African native the symptoms of trypanosomiasis are considerably aggravated by, and in many

Fig. 19. Cerebral trypanosomiasis. Appearance of patient in last stages of the disease. (*Dr. F. K. Kleine.*)

cases mistaken for, those of other diseases. The patient is invariably infected with malaria, ancylostomiasis, bilharziasis, and possibly filariasis, besides which much of the emaciation and the specific complications—septic rhinitis, otitis—are due to starvation and sheer neglect, as the patient, on showing symptoms of the disease, is usually expelled from the village by the inhabitants and left to die in the jungle, a terminal pneumonia or dysentery frequently supervening.

Mortality.—Although spontaneous recovery may take place in the early stages of trypanosomiasis, it is believed that when the disease has arrived at the stage of sleeping-sickness, death is inevitable. Corre has told us how native villages in Senegambia have been depopulated. What has occurred on the Congo, in Angola, and in Uganda, bears out this estimate of the gravity of the disease when it appears in epidemic form. We know that many islands in the Victoria Nyanza

have been completely depopulated. The population of the implicated districts of Uganda, originally about 300,000, was reduced in six years to 100,000 by sleeping-sickness.

Immunity.—Apparently man is immune to infection with the commoner trypanosomes of the big game, *T. congolense* and *T. vivax*, and also it is known that certain mammals are immune to trypanosomes which are pathogenic to others; thus *T. vivax* is pathogenic to horses and cattle, whilst rabbits, guinea-pigs, and mice are refractory. Although there is no direct evidence that man becomes immune after exposure to infection, yet there is no doubt that when the disease has lasted any length of time in a district, as in Southern Nigeria, the inhabitants exhibit a degree of resistance not seen in districts recently invaded.

The non-immune European generally suffers from the disease in a more acute form than does the Central African native under similar conditions. Russell and others who have studied the phenomena of immunity in man believe that the course of an infection with a pathogenic trypanosome depends upon the capacity of that trypanosome to vary serologically in the body so often that it defeats the possible variations of the host's defence.

Trypanocidal action of human serum on trypanosomes.—Following the interesting discovery by Laveran, in 1902, that normal human serum exerts a marked effect on the course of trypanosome infection in animals, a large amount of work has been devoted to this subject with the object of discovering an effective trypanocidal serum. Yorke, Adams and Murgatroyd have shown that normal human serum exerts a pronounced trypanocidal action *in vitro* at 37° C. on a number of strains of pathogenic trypanosomes, even when the serum is diluted 5,000–25,000 times; but in certain pathological conditions of the liver this power is lost entirely *in vitro*. The interesting fact has been observed that in the sera of certain normal sheep and rabbits, an active trypanocidal substance exists which, when mixed with normal human serum, inhibits the trypanocidal action of the latter. A curious and almost inexplicable feature is the fact that *T. rhodesiense*, *T. equiperdum* and *T. congolense* are rapidly destroyed *in vitro* by this method, but *T. gambiense* is apparently unharmed. Possibly in this observation lies the explanation of man's immunity to infection with the pathogenic trypanosomes of cattle and other stock.

Diagnosis.—Chronic irregular fever, more especially if associated with enlarged cervical glands and, in the European, erythema multiforme in a patient who has resided in tropical Africa at any time during the previous seven years, but more especially recently, suggests a tentative diagnosis of trypanosomiasis and detailed examination with this possibility in view. Diseases with which trypanosomiasis might be confounded are malaria, kala-azar, pellagra, syphilis, leprosy, lymphadenoma (Pel-Ebstein disease), and, in its later stages, beriberi.

The diagnosis of trypanosomiasis is made absolute by blood examination, but the serum-formalin reaction (*see* p. 191) is usually positive in well-estab.

lished cases of trypanosomiasis and therefore may serve as a rough guide for differentiation from other African fevers on a large scale (Hope-Gill, Morrison and Dye). Sicé and his collaborators have shown that there is a considerable diminution in the total serum proteins and the loss is mainly due to a decrease in serum albumin. The ratio of serum albumin to globulin is always less than it is in normal persons. Davis and Brown have recently worked out a specific immunity reaction in trypanosomiasis known as the "adhesion phenomenon." The reaction is characterized by the adhesion to the parasite, when acted on by the immune plasma *in vitro*, of blood-platelets and other bodies. The reaction is specific for different species of trypanosomes and the immune body shows a high degree of thermo-stability, and further research has shown that this test may be employed in recognizing species of wild game which act as reservoirs of *T. gambiense* infection.

Malaria, syphilis, and leprosy are easily excluded. As regards *beriberi*, there should be no difficulty if it be borne in mind that it is a disease of the peripheral, while trypanosomiasis is a disease of the central nervous system; that beriberi is non-febrile and trypanosomiasis febrile. *Kala-azar* and trypanosomiasis, especially in their earlier stages, may be more difficult to differentiate, but the presence of enlarged glands, local œdema, and erythema multiforme in trypanosomiasis, and their absence in kala-azar, suffice for distinction. Blood or gland-lymph examination, or, if this be negative, hepatic or splenic puncture, should establish the diagnosis.

General paralysis of the insane, cerebral tumour, forms of meningitis, especially encephalitis lethargica (often inaptly termed "sleepy sickness"), have features in common with trypanosomiasis and must be considered in diagnosis. The serum of some cases of trypanosomiasis has been said to give a positive Wassermann reaction; but later research has shown this to be due to a coexisting syphilitic infection.

The *microscopical diagnosis* of trypanosomiasis is sometimes difficult Anæmia, as well as a large mononuclear leucocytosis, usually occurs. A well-stained blood preparation exhibits, even to the naked eye, a remarkable clumping of the red corpuscles. Held up to the light, such a preparation has a peculiar granular appearance, produced, as can be seen on microscopical examination, by agglomeration of the corpuscles into heaps and clusters, the usual rouleaux arrangement being absent. This is known as auto-agglutination and is significant of, though not peculiar to, trypanosome infection. As a rule, the parasites in the peripheral circulation are few in number, many fields having to be hunted before a single example is discovered. Sometimes none can be found: rarely are they abundant. In the same case they are sometimes present, sometimes absent. Centrifuging citrated blood may prove of considerable assistance. Broden used 9 c.c. of blood to 1 c.c. of 6-per cent. citrate solution, centrifuged at first at 1,000 and subsequently at 1,500 revolutions for 10 minutes. The supernatant fluid of the latter is again centrifuged at 2,000 revolutions for 20 minutes, when the trypanosomes will be found in the precipitate. Letonturier, Tanon

and Jamot consider that this triple centrifugation method gives 92 per cent. of positive results.

Dutton and Todd emphasized the value of *lymph-gland puncture* and examination of the aspirated lymph as the most certain method, particularly in the earlier stages of the disease, when the glands are soft and the trypanosomes abound in the lymph, before they have become sclerosed. This method is said to succeed in 87·7 per cent. of cases. An ordinary hypodermic syringe suffices to aspirate a sufficiency of lymph, of which films are prepared and stained in the ordinary way. According to Kleine's statistics, out of 32 patients 24 had trypanosomes in their glands and blood, 4 had them in the glands but not in the blood, and 4 had them in the blood only. On the other hand, it must be emphasized that gland-puncture is not infallible, as a percentage of those infected fail to develop lymphatic reaction. Gland-puncture as a means of diagnosis should always be reinforced by the examination of thick blood-films; Pratti finds that palpation and puncture are of great value in itinerant practice. The enlarged glands may be unilateral or bilateral; or may be isolated and enlarged; sometimes they reach the size of a pigeon's egg and many gradations may be shown. Although the superficial glands may be easy to palpate, the deep ones may be more difficult. Three procedures for palpation are necessary: deep palpation, superficial palpation, and palpation by passing the palmar surface of the hand over the neck. Enlarged glands which may otherwise escape notice are detected by the radial side of the index-finger. Typical ones are described as being of the consistency of a ripe plum.

Cerebro-spinal fluid, obtained by lumbar puncture and centrifuged, affords another though not always a practicable means of finding the parasite; according to Broden, parasites may be demonstrated in this manner in 4·5 per cent. of cases, but if the trypanosome is not found, suggestive information may be obtained from a lymphocyte-cell count of the fluid, as this may be increased to over 1,000 per c.mm. The globulin content of the fluid is also increased.

The importance of puncture of the cerebello-medullary space in the diagnosis of trypanosomiasis has recently been emphasized by Tajera. Suboccipital puncture through the occipito-atlantoid ligament into the *cisterna cerebello-medullaris* is a simple procedure and is practically devoid of all risk.

Le Port states that the early changes in the choroidal plexus in trypanosomiasis are confined to the fourth ventricle, so that the immediate consequence is an interruption of the connections between the ventricles and the subarachnoid space. The only real orifices by which these two centres intercommunicate are by the foramina of Luschka, which lie between the cerebellar peduncles in the lateral angles of the fourth ventricle. These orifices are covered by the lateral choroidal plexuses of the ventricle. Obstruction of the foramina of Luschka results in separation of the subarachnoid space from the ventricles where the cerebro-spinal fluid is produced, and this

causes automatically a state of disequilibrium of the tension of the fluid between the two cavities. The intraventricular tension produced by the retention of the fluid in the ventricles may give rise to a syndrome which is responsible for the signs of the first stage of sleeping-sickness. Intraventricular hypertension manifests itself by headache, nausea and a degree of somnolence.

Sicé has proved that the earliest reaction resulting from meningeal lesions is cellular; at first it is slight and unaccompanied by clinical signs; usually it progresses slowly and the intensity of the meningeal lesions is shown by the number and character of the cells. The presence of leucocytes indicates that the lesions are active and, probably, recent. Plasma cells, dead cells and morular cells (Mott) indicate older and more chronic lesions. As the cellular reaction develops, so the albumin content gradually increases. Prognosis can be based upon the amount of albumin in the spinal fluid. This can be estimated by a number of different techniques, and the proportion of the albumin and the globulin in the cerebro-spinal fluid is considered by most authorities to run parallel to the number of cells present.

Failing discovery of the parasite by blood or lymph examination, recourse must be had to *animal inoculation*, 2–10 c.c. of the blood being drawn from a vein and injected. Of the ordinary laboratory animals, the most susceptible, and therefore most reliable, are the guinea-pig, the rat, the dog, and certain monkeys, *Macaca* and *Cercopithecus*. Such inoculations are of value as a test of recovery, as well as for diagnosis.

The intraperitoneal injection of olive oil in experimental animals aids in establishing the infection in cases where the parasites are scanty and consequently difficult to establish (Saunders).

The trypanosome is easily stained by most dyes, those in use for malaria work giving the best results. A $\frac{1}{6}$-in. objective suffices to find the parasite.

Treatment

Especially in the case of natives, preliminary treatment directed towards the eliminating of superimposed infections with ancylostomes or bilharzia is always advisable, especially on account of damage to the liver-cells which renders toleration of arsenical drugs difficult.

1. Treatment with "Bayer 205."—"Bayer 205" (urea of acid dimeta-aminobenzoyl-meta-aminoparamethylbenzoyl-l-naphthylamino-4-6-8 trisulphonate of soda) (*Germanin, Antrypol*[1]) was originally introduced in 1920, and this drug has been of great value in eradicating infection, especially during the earlier stages of invasion. Its therapeutic effects in man were foreshadowed by its remarkable trypanocidal action in artificially-infected laboratory animals. Bayer 205 is a white powder, easily soluble in water. The French equivalent is known as "Fourneau 309" (or Moranyl), the English as Antrypol, and their therapeutic action appears to be identical with that of Bayer 205.

[1] The preparation used in veterinary practice is known as "Naganol."

In animals infected with trypanosomes, Bayer 205 has been found to be remarkably atoxic, and the *dosis tolerata* has been estimated to be 160 times that of the *dosis therapeutica*, and when injected intramuscularly, or intravenously, it is lethal to *Trypanosoma brucei*, *T. gambiense* and *T. rhodesiense;* moreover, it has been found to exert a definite prophylactic action against these trypanosomes. In man, radical cures with this drug were originally reported by Mühlens, Menk, Kleine, Fischer, Low and the Editor. The average dose for man is 1 grm. dissolved in 10 c.c. of distilled water (or a 10-per-cent. solution), and it is injected intravenously. The total amount to effect a cure is about 10 grm., though the trypanosomes usually disappear and are not observed again after 5 grm.; sometimes, however, they do reappear in the peripheral blood. Usually the trypanosomes are no longer visible in the blood-stream some twelve hours after the injection, and it is necessary that this should be repeated at weekly intervals.

It is thought that the action of Bayer 205 lies in its power of rendering the trypanosomes fit for phagocytosis by the reticulo-endothelial cells, a kind of opsonizing effect. This opsonic action greatly enhances the effect of the drug in the living animal and thus explains its more efficient action *in vivo* than *in vitro.*

In an initial infection, directly the disease has been diagnosed, the best and most lasting results are obtained by giving bigger initial doses, such as 1 grm. on the first, third, tenth, and thirteenth days. Bayer 205 is retained in the tissues for a considerable period, so that the blood-serum, cerebro-spinal fluid and urine of the patient continue to exhibit trypanocidal powers when re-injected into trypanosome-infected mice. In exceptional circumstances individual doses of 1·5–2 grm. can be given to well-grown men.

Immediately after the injection of the drug, both the physical condition and mental outlook of the patient are remarkably improved. The drug is non-toxic to man, except that it has a cumulative action and is a kidney irritant, so that, after three or four injections, the urine contains albumin with the presence of small yellow, granular casts. This is the result of excretion of the drug *via* the urinary tubules, and this damage to the kidneys is not permanent, but lasts about six weeks. In some susceptible patients a toxic dermatitis—a red, itching and papular rash—develops usually after the third injection.

The intrathecal injection of Bayer 205 cannot be recommended, as pain, vomiting, headache, convulsions and twitchings may ensue after small doses, and advanced cases derive no benefit from this method. Although it is now recognized, almost universally, that "205" is the most active substance yet employed in the treatment of sleeping-sickness, as it has been shown to cure cases where all other known forms of treatment have failed, yet it appears to be incapable of destroying the trypanosomes when once they have entered the

grey matter of the brain. Kleine and Fischer originally reported on the treatment of 185 cases of *T. gambiense* infection in Africa, of which 80 per cent. showed a marked clinical improvement and were considered to be cured, and during the last year many series of cases have been published which bear out the original claims. Dye, in Nyasaland, reports favourably upon this drug in the doses advocated above, while Mayer (1928) published a critical review of the whole problem. The Editor has investigated three cases in Europeans in whom a permanent cure was effected after a total of 3–5 grm. of Bayer 205.

2. Treatment with tryparsamide.—*Tryparsamide,* the sodium salt of N-phenylglycineamide-*p*-arsonate, was introduced for the treatment of trypanosomiasis by Drs. W. H. Brown and Louise Pearce, of the Rockefeller Institute. (The French equivalent, " Fourneau 270 " (Orsanine) is acetyl-*p*-amino-*o*-oxyphenyl arsenic acid, and has been used extensively in French Equatorial Africa.) Tryparsamide should contain not less than 25·1 per cent. of arsenic in organic preparation.

When injected into the tissues it is quickly absorbed ; it may be given by either the intramuscular or the intravenous route. The chemotherapeutic index of tryparsamide, i.e., the ratio between the curative dose and the maximum tolerated dose, is 1 : 2. In the case of atoxyl, on the other hand, it is 1 : 1. The individual doses are large, varying from 1 to 4 grm. ; the optimum dosage is about 83 mg. per kilogram of body-weight. The drug has a marked effect upon the symptoms of the disease, especially when the nervous system is involved, and its chief value is the ease with which it penetrates into the cerebro-spinal fluid ; the trypanosomes, when present, disappear ; and furthermore, there is a great reduction in the round cells or lymphocytes in this fluid in cerebral trypanosomiasis, which is attributed to the high degree of penetrability of the drug. It is apparently capable of entering the brain substance, and of finding its way into the cerebro-spinal fluid. In an average case the initial dose should be 1 grm. in 10 c.c. of distilled water : subsequently it may be given in 2-grm. doses, three times weekly. A total dosage of 24 grm. is, as a rule, necessary.

Van den Branden has reported that 70–80 grm. are necessary to obtain permanent benefit in chronic cases. In the mildest cases he was able to obtain 57 per cent. apparent cures with a total of between 20–60 grm., but with 17·6 per cent. only in patients with trypanosomes in the cerebro-spinal fluid.

Tartar emetic injections, which are curative in some forms of cattle trypanosomiasis, are now mostly used to reinforce tryparsamide treatment in cases complicated by bilharziasis.

According to Chesterman, who has had a large experience of tryparsamide, the intravenous route is the most effective : the solution should not exceed 40 per cent., which is about the saturation point. Care should be taken to see that the water is not alkaline in reaction, as this produces precipitation. Intramuscular injection is also efficacious, but the solution should not exceed 20 per cent. Experience has proved that it is not wise to attempt " *therapia sterilisans magna*," as prolonged administration of the maximum tolerated dose gives the best results.

In early cases in adults a start should be made with 0·04 grm. per Kg. of body-weight and continued for a total of twelve weekly injections. Children up to twelve years of age, on the other hand, tolerate the drug well and should be given double this dose up to 0·08 grm. per Kg. of body-weight for twelve injections. A second course should be given as for adults.

Results of treatment with tryparsamide.—In early cases an apparent cure is almost invariable, but tryparsamide acts less certainly after prior administration of atoxyl or other arsenicals. In later cases figures vary, but, given good conditions in the absence of other debilitating diseases, in cases in which the degeneration of the central nervous system has not progressed too far and when the cerebro-spinal fluid does not contain too many cells, the drug gives gratifying results.

In more *advanced cases* in adults smaller doses up to 0·02 grm. per Kg. of body-weight should be given, on the fourth day 0·03 grm. per Kg., and on the eighth a course of 20 injections of 0·04 grm. per Kg. should be commenced. The course of ten injections should be repeated three months after the first. For children one should use doses of 0·06 grm. per Kg. If the drug is used in strengths of more than 20 per cent. by the intramuscular route, induration or abscesses result. In later cases a Herxheimer reaction with acute mania may ensue, should the initial dose be too large.

Optic neuritis.—Some patients are very sensitive to tryparsamide, and the Editor has found that it is especially those cases which have been previously treated with small quantities which are singularly apt to develop optic neuritis during a second course of administration of the same drug. There appears to be no agreement as to the amount of tryparsamide which provokes optic neuritis. The Editor has seen two cases where blindness ensued after 13 grm. had been injected. Lauterburg has reported a series of cases amongst which blindness occurred in 7·4 per cent. All the patients had received weekly doses of 2 to 3 grm. Advanced cases of the disease are much more prone to develop visual troubles than early cases and must be treated with caution. Objective signs of eye damage are not manifest early enough to enable one to prevent complete blindness from developing. The fundus remains normal for a long time and the pallor of the disc sets in quite late. The single dangerous sign is narrowing of the fields of vision and even this may be too late. Jamot reports that out of 25,638 patients treated with tryparsamide, 233 developed ocular trouble; in 30 there was amblyopia and in 17 amaurosis. Casten, in his studies of treatment of cerebral syphilis with tryparsamide, has not experienced the same degree of visual trouble in this disease. He classifies the ocular symptoms into (*a*) subjective, with blurring of vision, and (*b*) objective, with ocular damage. The first state comes on 15 to 30 hours after administration and lasts from one to three weeks; it always clears up on stopping treatment. The second becomes permanent, with diminution of the visual fields, and may lead to optic atrophy.

Premonitory symptoms may be photophobia, lachrymation, pain in the eyes and dimness of vision. It should be made the rule to test the vision of each patient before injection by detection of some small object. In any suspicious case the administration of arsenicals should be suspended and replaced by tartar emetic for one month, but the total course of tryparsamide should be completed if possible. Injections of ametox (May & Baker) or calcium thiosulphate may be given, though they do not apparently hasten recuperation. It must be remembered that the action of arsenic is often a delayed one and the symptoms of optic neuritis may progress even after cessation of arsenic treatment. Van den Branden and Appelmans find it

advantageous to associate sodium hyposulphite with *trypanarsyl*, and it is believed that the measure lessens the risk of visual disturbances. The same workers also state that in poisoning by inorganic arsenicals visual troubles are rare and late, whilst the symptoms and evolution are quite different from those observed in the course of treatment with atoxyl[1] and tryparsamide.

As a criterion of cure in addition to the physical improvement in the patient and in his mental capacities, a normal cell-count and albumin content of the cerebro-spinal fluid should be maintained for twelve months after treatment and should be regarded as sufficient evidence of cure after the cessation of treatment ; an excess of albumin, as well as of cells, may be noted for a short time, but disappear later.

Other arsenical compounds.—Van den Branden has reported on a trial of *etharsanol* (monosodium salt of 2-*p*-arsono-arsilino-ethanol) and *proparsanol* (monosodium salt of 3-*p*-arsono-anilino-proponol), each of which contains 20 per cent. of arsenic. These drugs were injected in doses of 2 grm. and their action was found to be comparable to that of tryparsamide, but both appear to produce optical disturbances more readily than the latter.

Yorke, Murgatroyd, Glyn-Hughes and Ross have tried out sodium succinanilomethylamide-*p*-arsonate (*neocryl*) and find that it compares favourably with tryparsamide in being somewhat less toxic and possessing a somewhat greater trypanocidal activity. The doses are similar to those of tryparsamide. This product has been tested out by Murgatroyd on the Gambia with satisfactory results.

N-phenylglycineamide-p-arsonic acid, of which tryparsamide is the sodium salt, may be given by the mouth, which, in dealing with large numbers of natives, is a simpler method. In contrast to tryparsamide it is well tolerated by this route and causes disappearance of trypanosomes from the blood and cerebro-spinal fluid, though in a slower and less dramatic manner. The tablets (supplied by Messrs. May & Baker) are crushed in water and swallowed. The dosage is twice that of tryparsamide by the parenteral route and has the advantage of being less liable to produce optic neuritis, any excess manifesting itself in gastro-intestinal irritation and elimination of the arsenic through diarrhœa.

Gruhzit, Lindsay, Hendricks and Dodd find *Mapharsen* satisfactory. This is meta-amino-parahydroxyphenyl-arsine oxide and is believed to be the compound elaborated in the body after injection of arsphenamine. The initial dose is 40 mg. per kilogram body-weight for a woman, and 60 mg. for a man.

3. Combined treatment with Bayer 205 and tryparsamide. – In the comparatively few European cases which reach England at the present time, the Editor has recorded some striking recoveries by the employment of a combination of Bayer 205 and tryparsamide therapy. There is no doubt, from the clinical aspect, of the reality of the experimental work of Yorke that the pathogenic trypanosomes readily become drug-fast, and that this resistance (*see* p. 160) is developed towards Bayer 205 (but more slowly) as it is to the arsenical drugs. The Editor has reported upon the histories of 11 Europeans in

[1] On account of its liability to produce optic neuritis the routine use of *atoxyl*, which was formerly extensively employed, has been abandoned.

which success was obtained by Bayer 205 therapy in cases which had resisted tryparsamide and *vice versa*. The conclusion which can be legitimately drawn from clinical experience is that, when once a clinical and parasitological relapse has taken place after an initial course of treatment with one trypanocidal drug, it is little use persisting with even larger doses of the same, but that an immediate change should be made and a substance of entirely different chemical constitution substituted. In the Editor's opinion, preliminary Bayer 205 treatment in maximum tolerated doses should be followed by tryparsamide injections in moderate doses—2-grm. doses twice weekly (or 4 grm. per week). Chesterman, in his latest communication, advocates two or three large doses of Bayer 205 (3 doses of 1·5 grm. for an adult at three- or four-day intervals) followed by 6–8 weekly injections of medium doses of tryparsamide, i.e. 0·07 grm. per kilogram of body-weight for children; 0·055 grm. per kilogram for young adolescents; and 0·045 grm. per kilogram for adults.

Between these two courses a rest of ten to fourteen days should be allowed until the urine becomes free from albumin before administering tryparsamide. Alternating injections of tryparsamide and Bayer 205, with intervals of three days, have also been given with good effect. This method has been adopted by Maclean in Tanganyika, Duke in Uganda, and Dye in Nyasaland, and their results have been encouraging.

Other preparations undergoing trial.—Lourie and Yorke and Browning announce that *synthalin*, a guanidine compound, exerts a trypanocidal action by an entirely new principle. It is known that trypanosomes require for their metabolism a large quantity of sugar. Synthalin produces hypoglycæmia and in this manner causes destruction of these organisms.

On the same lines they find *undecane diamidine* effective; this, also a guanidine, of an entirely different constitution from all other known trypanocidal substances, is of considerable academic interest.

General considerations.—The exact manner in which the trypanocidal drugs act provides a problem which has not been satisfactorily settled. One aspect of the question is the matter of drug-resistance (*see* p. 160). Van Hoof, Henrard and Peel find natural drug-resistance in the case of *T. gambiense* to tryparsamide much commoner than is generally believed. It appears that a trypanosome can suddenly acquire a certain degree of arsenic-resistance by passage through unaccustomed hosts. Murgatroyd, Russell and Yorke consider that trivalent arsenical compounds owe their therapeutic activity entirely to the fact that their highly trypanocidal substances circulate unchanged in the blood-stream and that tryparsamide owes its activity to the fact that it is gradually reduced in the blood, and possibly also in the tissues, into its corresponding trivalent compound. The trivalent compounds also escape from the blood with remarkable speed, and consequently it can be explained that the trypanocidal titre following

an injection of tryparsamide never rises beyond modest limits on the ground that, as fast as the tryparsamide is reduced to its trivalent form, it is eliminated from the blood-stream

Prophylaxis.—The indications for prophylaxis are based principally on the habits of *Glossina palpalis,* and the existing conditions as regards the presence of the infection in a locality.

In endemic regions the fly areas should be located and avoided. If such regions have to be traversed, the journey should be made during dark nights, when tsetse flies do not feed, or with such precautions as are used by the natives for the protection of their cattle in nagana-infected spots. Those who are compelled to live in tsetse regions should have their houses and persons carefully guarded against the fly. Manifestly, it is desirable—whether it is feasible is another question—to avoid localities in which the natives are affected, and to prevent infection of the local tsetse flies by people who have trypanosomes in their blood, by means of mosquito-netting, or by other measures, such as removing them from the usually very limited fly area to some neighbouring fly-free spot. Movement of infected individuals to hitherto uninfected countries must necessarily be attended with great risk of the introduction of the disease. Whether such movement can be prevented in savage lands depends greatly on local circumstances. Wherever possible it should be prevented. Dutton and Todd suggested that an easily ascertained condition, more or less general in trypanosomiasis—namely, enlargement of the cervical glands—should be employed in eliminating dangerous individuals. Many years ago slave-dealers adopted such a method to shield themselves from loss. As a rough test it has some value. But in some cases of trypanosomiasis the glands are not appreciably enlarged at all times. Moreover, as they are often enlarged in other conditions, injustice might be done in enforcing such a measure.

Hodges in Uganda found that the fly ground proper is always a very narrow strip, not more than ten to fifteen yards wide, and always along the water's edge, and that the insects very rarely extend their feeding beat sixty yards beyond this, whether on the land side or on the water side. It is true they may follow with great persistency a man who has just passed through this narrow belt, for several hundred yards, rarely for half a mile ; but it is obvious that if the ten or fifteen yards at the water's edge be made unsuitable for the fly, as can be done by clearing it of jungle, there will soon be no flies to follow human beings, and the place will become safe. Therefore, where feasible, fly spots, where there are landing-places, ferries, wells, or roads, should either be avoided altogether or be cleared of jungle for some yards—to be safe, thirty—from the water's edge. This is a practicable measure of proved value in Uganda.

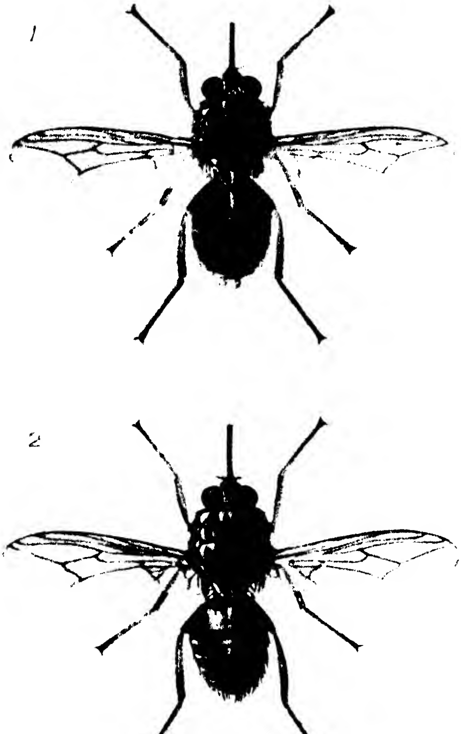
Van Hoof reports that by systematic injection of infected natives with tryparsamide a progressive lowering of the index of new infections is taking place in the Belgian Congo ; but that a constant watch is

necessary to maintain this position. If vigilance is relaxed, the disease may flare up again with the intensity of an epidemic.

Chemoprophylaxis.—With the advent of Bayer 205 it was hoped that an efficient prophylactic under natural conditions had been procured. So far this method has not given very encouraging results; although a prophylactic injection with Bayer 205 does not prevent actual infection, it does, according to Kleine, definitely mitigate the pathogenicity of the infecting trypanosome and, similarly, prophylactically-inoculated animals remain in good health and general condition when subsequently infected with *T. brucei*. Fourché, on the Congo, considered that the injection of 1 grm. in the case of adults, and 0·3 to 0·75 grm. in the case of children and adolescents, by the intravenous route, had a definite prophylactic value, which was observed over a period of seven months. Van den Branden inoculated all the inhabitants of a village in the Belgian Congo with the following doses: adults 1 grm.; adolescents 0·5 grm.; children 0·25 grm.; and infants 0·18 grm.—each receiving two injections. At a subsequent visit to this area six months or more afterwards only one case of trypanosomiasis was found to have developed in this village. Duke's statistics on the chemoprophylactic treatment of Europeans and natives of Uganda with injections of Bayer 205 seem to indicate that the prophylactic action may last for at least three months, possibly longer. Olovitch (1937) reports very favourably on the mass injection, or "moranylization," of the native population on the Belgian Congo. Schilling, Shreck, Neumann and Kunert have endeavoured to produce immunity to reinfection with pathogenic trypanosomes by primary inoculation with feebly pathogenic strains of the homologous organisms. This work has been confirmed by van Saceghem, who has produced a state of *premunition* to cattle trypanosomes in these animals, but it is doubtful whether these methods are applicable to man.

Drug-resistance and its transmission through the tsetse.—An important bearing on the question of prophylaxis of trypanosomiasis has been opened up by the work of Yorke and his collaborators on drug-resistance, showing that trypanosomes readily become drug-fast, especially to the arsenic compounds, such as atoxyl, arsacetin and tryparsamide, but less easily to antimony, and that the reaction develops very quickly, within a period of 4–8 weeks. They have proved an even more important and far-reaching fact—that strains of trypanosomes possessing a high degree of resistance to the aromatic arsenicals are transmissible by glossina (*transmission of an acquired character*) and, moreover, that this acquired character of drug-resistance remains unimpaired after two successive passages through the tsetse.

Other prophylactic measures.—Brilliant results have attended the efforts of the Portuguese to combat sleeping-sickness in the island of Principe, where the annual mortality from the disease amounted to 83 per thousand of the population, and the local industry (cocoa) was



1. *Glossina palpalis*. 2. *G. morsitans*.

TSETSE-FLIES.

Plate V

1, Parasites enclosed in endothelial cells in film from spleen puncture, stained with Leishman. 2, Free forms from spleen. 3, Blood-platelets in same film for comparison. 4, Parasites enclosed within splenic pulp cells, as seen in section, stained with hæmatoxylin. 5, Parasites in plasma and endothelial cells in intestinal mucosa. 6, Diagram of Leishman-Donovan body, highly magnified.

LEISHMAN-DONOVAN BODIES IN KALA-AZAR.

× 1000

threatened with extinction. Besides jungle-clearing, drainage, blood examinations, segregation of the infected, and destruction of possible animal reservoirs of the trypanosome, coolies, dressed in white and carrying on their backs a dark cloth smeared with birdlime, were sent into the jungle, and every night the flies caught were removed and counted. In three years 470,000 glossinæ were caught. As a consequence of this combination of sanitary measures the fly and the sleeping-sickness were exterminated. Of course, it was only the complete isolation and the limited size of the island that made such a result possible.

A complete scientific prophylaxis can be indicated with certainty only when we have full knowledge (1) of the habits of the tsetse flies and of the reasons for their restriction to very limited and apparently capriciously distributed areas; (2) of what vertebrates under natural conditions are normally hosts of *T. gambiense*.

Attempts recently made by Lamborn to introduce a predatory insect which would destroy the pupæ of glossina have so far been attended with but a moderate degree of success. In 1914 Austen suggested the introduction of the chalcidiid—*Spalangia*—into tracts where *G. morsitans* is a pest. Consequently one species of chalcidiid (*Syntomosphyrum glossinæ*) has been bred in large numbers in the laboratory and distributed over an area of Lake Nyasa of about 42 square miles. In the course of three months it was found that 8·7 per cent. of glossina pupæ were parasitized by *Syntomosphyrum*. Roubaud and Treillard have been carrying out some encouraging experiments by infecting *Glossina palpalis* with a cocco-bacillus which is pathogenic for muscidæ.

In Uganda and elsewhere, principally in order to preserve the hitherto uninfected from trypanosome infection, the Government removed the entire population of the Sesse Islands and neighbouring shore of Victoria Nyanza to fly-free areas in the interior. It was hoped that, the human source of trypanosome supply being thus denied them, the tsetse flies would cease to be infective. Unfortunately, this hope has been disappointed. Three years after the depopulation of the districts involved, Bruce ascertained that local flies could still convey the disease to laboratory animals. Manifestly, *T. gambiense* can flourish under natural conditions in vertebrates other than man, especially on the situtunga antelope.

Following on the opening up of Central Africa by motor roads and the development of motor traffic, a new problem in the spread of trypanosomiasis has presented itself which applies to *gambiense* as well as to *rhodesiense* infections. Jack has shown the tendency of these flies to follow up moving objects and to settle on the backs of pedestrians and cyclists and under the hoods of motor cars. On pedestrians these flies may be carried 10, on motor cars, 50 miles a day. When the moving object stops, the flies move away and seek shade nearby. It has been found necessary to restrict vehicles (including cycles leaving fly areas to fixed routes. At the point of

exit notices are placed stating that motorists and cyclists must submit to prescribed measures. Native cyclists are cleansed of flies, in special gauze cages. As regards motors, the vehicle is fumigated with "Flit" and the passengers are groomed with insect-nets.

Fly traps.—Harris, an entomologist, has had very considerable success with a tsetse-fly trap of his own devising, the materials for each costing about 30s. The trap consists of a framework of light wood, covered by hessian cloth, being roughly triangular in section, with a flat top, 6 ft. long by 3 ft. wide, the sides converging to about 3 in. apart with a narrow open slit along the bottom, the ends being vertical and triangular. The body is slung on wires so that the open slit is 48 in. from the ground. To the flat upper surface a transparent cage of wire gauze, of a mesh sufficient to retain a fly, is fixed; where the cage fits to the flat surface the cloth is removed and the wire so arranged that the flies cannot return to the hollow body of the trap. These traps are suspended on the sunny margins of evergreen bush haunts of the flies, and so placed that they throw a separate shadow, and it has been found that, in suitable weather, each trap will kill 100 to 200 flies daily. This trap has been specially successful in catching large numbers of *Glossina pallidipes* and *G. palpalis*, but is not so successful with *G. morsitans*.

Swynnerton had been using a somewhat similar kind of trap since 1922, one containing a live calf to which the flies are attracted by scent. The most effective is a moving screen carried by fly-boys, who are able to catch with a net practically every fly that the screen attracts. *Glossina pallidipes* and *G. palpalis* can readily be caught by any suitable trap, but other species (*G. morsitans* and *G. swynnertoni*) are less responsive. Considerable care is required in the siting and setting of traps, which should be placed as conspicuously as is possible.

Swynnerton's policy for dealing with the disease and the tsetse menace comprised three main lines of attack: firstly, segregation and treatment of trypanosomiasis cases with a view to sterilizing the blood of infected persons and thereby cutting off some source of supply, or reservoir of the parasite; secondly, abolition of contact between man and the fly by removing natives from areas heavily infected and establishing them in cleared country, at the same time controlling their movements by issue of permits; thirdly, clearing of bush along the lines of communication and extending agricultural operations.

[For a detailed description of the tsetse flies (Plate V), *see* pp. 1002–1005.]

Rhodesiense Sleeping-Sickness

The trypanosome found in cases of human sleeping-sickness originating in Rhodesia is considered to have certain peculiarities when inoculated into the rat. This fact, together with the greater virulence of the disease as it occurs both in man and in laboratory animals, and the greater resistance this trypanosome exhibits to arsenical treatment,

led Stephens and Fantham to separate it as a distinct species under the name of *T. rhodesiense*, in 1910. Later, it was proved that the parasite is transmitted by *Glossina morsitans* (Kinghorn and Yorke), not by *G. palpalis*. Some authorities continue to regard *T. rhodesiense* merely as a human strain of *T. brucei*, the common parasite of big game.

Kleine regards *T. rhodesiense* as the form taken by *T. gambiense* when introduced into a new area and transmitted by tsetse flies of the *morsitans* group, and regards it as distinct from *T. brucei*; whereas Duke regards *T. rhodesiense* and *T. brucei* as the same; Lavier holds that *T. gambiense*, *T. rhodesiense* and *T. brucei* are one and the same species. The conclusion of the International Commission on Human Trypanosomiasis was that *T. rhodesiense* represented *T. gambiense* transmitted by a different species of glossina, viz. *G. morsitans*.

Yorke and his collaborators have pointed out that in the selective cytolytic action of normal serum on trypanosomes and the resistance of *T. gambiense* to this action, to which *T. rhodesiense* so readily succumbs, may lie the explanation of this problem. As far as this test is concerned, *T. rhodesiense* and *T. brucei* would appear to be identical, a view which this worker has always held to be correct. The serum resistance of *T. rhodesiense* is not a fixed or stable character, but one which is readily acquired and quickly lost.

Duke has now shown that strains of *T. rhodesiense* maintained in animals may eventually lose their power of infecting man, and this effect is ascribed to prolonged passage through guinea-pigs. On the other hand, *T. gambiense* when kept for fourteen years in laboratory animals was unimpaired in its pathogenicity for man, though it had completely lost its transmissibility by *Glossina palpalis*. Duke therefore considers that eventually *T. rhodesiense* may revert to a form indistinguishable from the mild *T. brucei*. Therefore, *T. gambiense* and *T. rhodesiense* are to be regarded as particular strains of *T. brucei* which have become more or less adapted to life in the blood of man and it is believed that the resistance of man to *T. brucei* is by no means absolute.

Corson (1936) passed *T. rhodesiense* from the human source through a series of sheep by *Glossina morsitans* and eventually back into his own body, and by this self-sacrificing experiment sought to disprove the contention put forward by Duke.

Geographical distribution.—This form of sleeping-sickness occurs in North-Eastern Rhodesia, especially in the Luangwa Valley, about the southernmost limit, 14° S.; in the south-eastern portions of Tanganyika Territory up to 10° S.; in Portuguese East Africa; in Nyasaland, especially in the region south and west of Lake Nyasa: in fact, its distribution closely corresponds with that of *G. morsitans*. (Map II.)

Ætiology.—In human blood (Fig. 20–*1*, *2*), *T. rhodesiense* is morphologically indistinguishable from *T. gambiense*; but if it is passed through the rat or guinea-pig, a small but variable proportion of the parasites, especially the stumpy forms, will be seen to have their nuclei located posteriorly to the

kinetoplast—that is to say, at the non-flagellar end of the organism (Fig. 20-*3, 4, 5, 6*).

A good deal of energy and work have been expended in attempting to prove and disprove that *T. rhodesiense* is no other than a strain of *T. brucei* inoculated into man. When injected into rats, *T. brucei* exhibits the same proportion of posterior-nucleated forms as *T. rhodesiense* (Bruce). Taute and his fellow-workers have disproved this theory somewhat conclusively by inoculating themselves and 129 native porters with dog's and mule's blood containing *T. brucei*—with a negative result, while rats, dogs and a goat inoculated with the same blood at the same time, succumbed. These experiments, they claim, definitely disprove that *T. brucei* is in any way pathogenic to man.

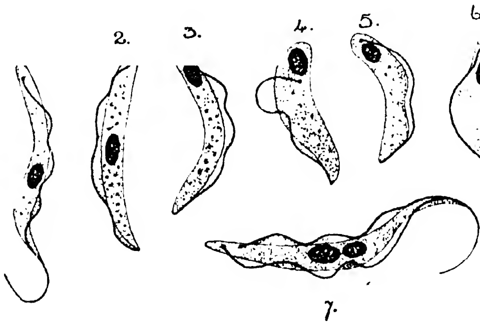


Fig. 20.—Forms of *Trypanosoma rhodesiense*. (*After Laveran.*)
1, 2, Normal forms in blood of man; 3–6, various stages of posterior displacement of the nucleus; 7, a dividing form.

RESERVOIR-HOSTS

Three species of antelope, the waterbuck, reedbuck, and duikerbuck, are usually regarded as reservoir-hosts of the *rhodesiense* form. The common waterbuck has been artificially infected with the human *T. rhodesiense*, and though they themselves show no signs of disease it has yet been proved that their blood is infective to monkeys (Weck). Corson has succeeded in infecting the small dik-dik and also the hyrax with *T. rhodesiense*.

The outbreaks reported by Duke and Swynnerton near Mwanza in 1922, and by Dye in the south-eastern districts of Tanganyika Territory in 1927, render it probable that in these instances the so-called *T. rhodesiense* was conveyed directly from man to man by *Glossina swynnertoni* without the intervention of any big game.

Symptoms are similar to those evoked by *T. gambiense*, though febrile paroxysms are more frequent, and severe glandular enlargement is not often met with. The disease generally runs a much more rapid course, and fatal symptoms usually supervene within a year of infection, death taking place from convulsions. Acute mental symptoms, such as mania, are frequently observed.

Buchanan has observed that rapid emaciation, weakness, fever

and œdema constitute the most obvious signs of toxic action resulting from this trypanosome infection, whilst careful observation on the heart showed that in nearly every one there is a marked effect on the cardio-vascular system producing irritability and tachycardia.

Lamborn and Howat (1935) have shown that very mild and almost symptomless infections in natives of Nyasaland may occur. The parasites are found to be quite numerous in the blood-stream, but are not seen in the glands or in the cerebro-spinal fluid. On inoculation into animals a virulent infection ensues. Similar cases have been reported by Woolf in the valley of the Rovuma River in Tanganyika in 1910, and the discovery of such a human carrier was associated with definite outbreak of trypanosomiasis.

Diagnosis is the same as for *T. gambiense*. Possibly the parasites are more easily demonstrated by lymphatic-gland puncture.

Corson has shown in a self-inflicted experiment that a local circular erythema with a darker and slightly tender centre is a useful indication of an infective bite by glossina in light-skinned people.

Treatment

Atoxyl, tryparsamide and antimony preparations (*see* pp. 155–157) which are of use in *T. gambiense* infections appear to be relatively powerless in *T. rhodesiense* cases. Successes have been reported after massive intravenous doses of antimony tartrate when treatment is commenced early and a total of over 500 gr. has been administered (Daniels and Newham). Unfortunately, some of the apparently cured cases which have been recorded have subsequently relapsed.

The treatment with Bayer 205 (*Germanin*) is more hopeful, and remarkable successes have so far been recorded; in fact the drug appears to exert a much more immediate and specific action than in *T. gambiense* infections. Dye, in Tanganyika Territory, reported that intravenous injections on the first, third and fifth days, subsequently at intervals of five to seven days till a total of 7 grm. has been administered, resulted in the disappearance of the trypanosomes from the peripheral blood within twenty-four hours. The drug no doubt has a remarkable sterilizing effect in early hæmic infections.

The Editor has had two striking examples in young Europeans, both of whom were permanently cured with 2 grm. of Bayer 205 given within fourteen days from the time the infection was detected: one of the two had entirely failed to respond to tryparsamide. The latter drug has no action on *T. rhodesiense* comparable to that on *T. gambiense* infections (Dye). Corson, in Tanganyika, believes that tryparsamide only has a place in the treatment of *rhodesiense* infection as an after-treatment when the symptoms and signs have abated.

There is some evidence that in man a strain of Bayer 205-fast trypanosomes may be evolved, as Morgenroth and Freund have shown takes place in mice, and Kleine and Fischer in monkeys and cattle. One European case under the Editor's care relapsed and died after 33 grm. of Bayer 205 had been injected, and the trypanosomes reappeared in the blood and cerebrospinal fluid apparently uninfluenced by the drug.

Prophylaxis.—Prompted by the results of his investigations of the hypothesis that big game act as a reservoir for *T. rhodesiense*, Yorke advocated the extermination of this fauna, but recent investigations tend to show that these conclusions were premature and that man himself may often be the chief source of infection.

The other prophylactic measures are the same as those advocated for *T. gambiense*.

Prophylactic injection of Bayer 205.—Duke (1934) has shown by experiments on human volunteers that the prophylactic action of Bayer 205 is more effective against *T. rhodesiense* than against *T. gambiense*. He finds that a single dose of 1 grm. of Bayer 205, given intravenously, will protect a man for at least 113 days from infection by tsetse carrying *T. rhodesiense* in cyclical development, and that the administration of a second similar dose three weeks after the first enhances its protective action. Within certain undetermined limits the protective effect may be directly proportionate to the number of doses given; but it is advisable that inoculations should be repeated every three months. Probably the natural sensitiveness of the mammal to the trypanosome plays an important part in determining the duration of protection conferred by Bayer 205, the more susceptible monkey receiving less protection per dose per kilogram of body-weight, than man, who is more resistant.

Note to the student.—As the prophylaxis of trypanosomiasis is interwoven with a knowledge of the life-history of the tsetse fly and its breeding habits, the student is referred to the section on Entomology where this subject is dealt with (p. 1004).

It is also necessary that he should have a working knowledge of the appearance and pathogenic properties of trypanosomes which are morphologically similar to those found in man (*see* p. 872).

II. SOUTH AMERICAN HUMAN TRYPANOSOMIASIS

Synonyms.—Chagas' Disease; Derrengadera.

Definition.—This is usually an acute, and more rarely a chronic disease, caused by *Trypanosoma* (*Schizotrypanum*) *cruzi*, and disseminated by certain reduviid bugs. The acute stage of the disease is characterized by diarrhœa and enlargement of the lymphatic glands, the thyroid, and the spleen, accompanied by cerebral symptoms. The chronic form is marked by special symptoms, according as the heart or other important organs are most invaded by the parasite.

History.—The history of this disease is interesting. Originally the trypanosome was found in the blood of a monkey which had been subjected experimentally to the bites of *Panstrongylus* (*Triatoma*) *megistus*, and subsequently in 1909 Carlos Chagas found the same trypanosome in children in Brazil; at the same time he traced the development of *T. cruzi* in the reduviid bug *Panstrongylus megistus*, which transmits the disease to man and domestic animals, although allied species of bug, and even other arthropods, have been

found by Brumpt to have the power of transmitting the infection, at any rate under experimental conditions. The most complete work on this subject is the monograph by Dr. F. L. Nino, Buenos Aires, 1929.

Geographical distribution.—In the provinces of Minas Geraes, São Paulo and Goyaz in Brazil ; in the states of Trujillo and Miranda in Venezuela ; in San Salvador (Segovia) ; and in the Western Argentine in Tucuman and Jujuy (Mühlens and Zuccarini). It has also been found in children in Cordoba (Argentina) and in the Catamarca province (Geoghegan). (Map I.) The disease has also recently been found in Panama and in Guatemala (Reichenow), in Bolivia and Peru (Escomel), in Venezuela and San Salvador (Tejera), and in Uruguay (Talice).

That this trypanosome is probably a more frequent infection than has hitherto been suspected, is shown by the fact that Noguchi (1924) recorded the isolation of a trypanosome from the blood of a yellow-fever patient in Colombia.

Trypanosoma cruzi, or trypanosomes resembling it, have been found in bugs (*Panstrongylus*, *Triatoma* and *Rhodnius*) in California, but they apparently do not transmit the disease to man in these regions. It remains to be seen whether *T. cruzi* is confined solely to the New World, for Malamos has discovered this trypanosome in monkeys imported into Germany from the Dutch East Indies, where *Triatoma rubrofasciata* is known to occur and is infected with a trypanosome (*T. conorrhini*).

It is remarkable, as pointed out by Hoare, what a comparatively rare human disease this is, considering its widespread range in the insect intermediary.

Ætiology.—During the febrile attacks the parasite, *T. cruzi*, can be found only sparingly in the blood, though in the acute disease, as seen in children, it is more abundant. In chronic cases, in which the clinical symptoms may be puzzling, they are apparently absent. Apparently in human beings this is a disease of childhood, but in Panama a case has been found by Ludeberg in a man of seventy-seven.

This trypanosome was at first referred to a separate genus, *Schizotrypanum*, on account of its distinctive method of multiplication in the human body. In place of the longitudinal division which occurs in other species of trypanosomes, this parasite proliferates in the cells of the internal organs, especially in the interior of striated muscles, such as the heart. Two forms, one slender, the other broad, are met with in the peripheral blood. In the internal organs multiplication takes place by schizogony (Fig. 21) at a very rapid rate, the resulting forms resembling leishmania bodies which, four days later, become transformed once more into trypanosomes that invade the blood-stream. (For a complete account of the parasite, *see* Appendix, p. 874.) This trypanosome, as it occurs in the blood, can be distinguished from other human trypanosomes by reason of its peculiar "C"-shape. It is by no means certain whether it is related to, or identical with, *Trypanosoma vespertilionis* in bats.

T. cruzi is easily cultured on N.N.N. medium, in which it assumes the stunted forms usually seen when it is found in its definitive hosts.

The reservoir-hosts of *T. cruzi* are animals peculiar to the country in which the disease occurs; these are various species of armadillo and opossum (*see* p. 173).

Transmission.—The adult trypanosomes are ingested by the intermediary invertebrate host, *Panstrongylus megistus*,[1] either in the larval, the nymphal, or the adult stage of this bug (Fig. 349, p. 1016). After they have passed through many stages in the intestinal canal, in a period of 8–10 days, fully formed trypanosomes known as "metacyclic" forms reappear in the hindgut and are passed out through the fæces of the insect. Infection of man, therefore, probably takes place

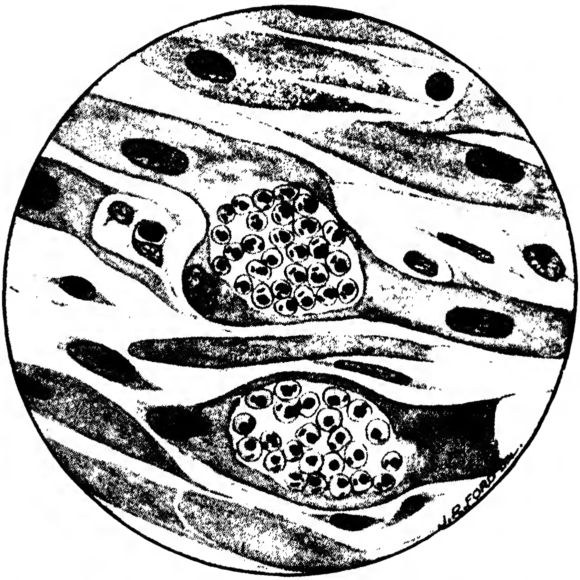


Fig. 21.—*Trypanosoma cruzi*: **schizogony in heart-muscle.**
(*From a preparation by J. Gordon Thomson.*)

through the insect defæcating into the wound caused by its bite. The original idea of C. Chagas (1909) that infection is conveyed by the bite of the Panstrongylus has not been confirmed, and Mayer has stated that infection may be conveyed through the bug in a hereditary manner. In the Northern Argentine the common host appears to be the *Unchuca* (*Triatoma infestans*); in Uruguay *T. rubrivaria*, but other species of the genus *Panstrongylus*, *Rhodnius prolixus* and *Triatoma* can transmit the infection.

Under experimental conditions, all laboratory animals can be

[1] This bug has been given various synonyms at various times, and is described in the literature as *Triatoma megista*, *Lamus megistus*, and *Conorhinus megistus*.

readily infected, and under natural conditions the domestic cat has been found to harbour this trypanosome. Developmental forms of this trypanosome have been found in bugs as far north as Utah (*see* p. 167). In infected animals transmission from the parent to the offspring *in utero* can apparently take place (C. Chagas), but originally he affirmed that in humans congenital transmission frequently takes place.

Pathology.—The post-mortem appearances have been described in children dying of this disease. The heart is usually enlarged and there is an excess of pericardial fluid of a yellow or greenish colour sometimes containing a few fibrinous flakes. In microscopic sections there is evidence of diffuse myocarditis and between the muscle fibres there is extensive infiltration of lymphocytes, plasmocytes, macrophages and round cells. There is enlargement of the spleen, parenchymatous degeneration of the liver, and general enlargement of the mesenteric glands. The thyroid gland, as a general rule, is congested and hypertrophied. There is general infiltration of the subcutaneous tissues and thickening of the serous membranes. Subserous ecchymoses are common, and small hæmorrhages in the brain and spinal cord have been described. The skeletal muscles appear to be the seat of election for multiplication of the parasite, and the changes in the voluntary muscles are essentially similar to those which occur in the heart. The gross lesions in the various organs are due to the presence of the parasite. Under the microscope, cyst-like cells can be found, particularly in the striated muscular fibres, and in those of the heart. When the suprarenal glands are affected, pigmentation of the skin and other evidence of Addison's disease have been observed. The blood does not show great changes, as a rule; the trypanosome may persist without causing severe anæmia for a very long period, and they have been found in the blood of a man twenty-five years of age, who exhibited no marked symptoms of disease.

Symptoms.—There have been noted in the published accounts of Chagas' disease considerable discrepancies regarding its distinctive features, so that during recent years a note of hesitancy has been observed about recognizing any peculiar syndrome as being distinctive. Some authorities believe that there are no distinctive clinical features; thus Miller reports that the symptoms and signs of the Panama cases were essentially negative. The trypanosomes disappeared from the peripheral blood without the action of any specific drug in the course of a few weeks.

Chagas (1934) has now described the experimental inoculation of a patient suffering from incurable malignant disease. An intermittent pyrexia lasted for three weeks. Trypanosomes appeared in the blood on the thirty-eighth day. There were no striking clinical manifestations.

Romaña has recorded unilateral conjunctivitis with œdema (Romaña's sign) as an early and distinctive sign of infection with

T. cruzi (Fig. 22), and has conjectured that the conjunctiva might be a port of entry for the trypanosome, and now E. Chagas has proved this to be true, experimentally, by placing the excreta of bugs on the conjunctiva of rabbits. In the case he published the attention drawn to the unilateral ocular condition led to the discovery of the trypanosome nature of the disease.

Caceres and Inaguirre first noted, in a case of acute Chagas' disease in a boy of five years of age, localized œdema of the eyelids, malar and temporal regions.

The following clinical syndromes have been described by Chagas and his co-workers: (*a*) *The acute form* usually occurs in infants of about one year. A fever exhibiting slight nocturnal elevations persists as long as the parasite occurs in the blood. In very severe cases it may reach 104° F., especially in infants, and there is often general anasarca. The face is puffy, the thyroid gland greatly hypertrophied, and the superficial lymphatic glands, especially the axillary and inguinal, are enlarged. Whether the hypertrophy of the thyroid is an essential part of the disease is by no means clear, as goitre is extremely common in those parts of Brazil in which this disease occurs, and there is little doubt that many of the cases are trypanosome disease superimposed upon epidemic goitre. The puffiness of the face, accompanied by conjunctivitis, is said to be so characteristic as to be almost diagnostic and on this account it was formerly confused with ancylostomiasis. The liver and spleen are both enlarged. The thyroid enlargement is one of the earliest symptoms, and has been observed in breast-fed children two to three months old. In the terminal stages the child develops symptoms of an acute meningoencephalitis; death generally takes place within a month of the onset, but should the child survive, the disease passes into the chronic form. Yorke remarks that myocardial degeneration and heart failure are the commonest cause of death, as the parasite evinces a predilection for the heart muscle, causing bradycardia with peculiar cardiographic tracings and low or absent P and T waves.

Fig. 22.—Unilateral conjunctivitis as an early sign of infection with *T. cruzi* (*Publicatión No. 24, Universidad Buenos Aires*).

(*b*) *The chronic form.*—According to Brumpt, Chagas' disease in the chronic form may be subdivided into the following varieties,

viz. pseudo-myxœdematous, myxœdematous, cardiac, and nervous. The pseudo-myxœdematous type is frequent in children up to 15 years of age; they suffer from a chronic cachexia, irregular fever, cardiac hypertrophy, and tachycardia. There are usually other myxœdematous symptoms, as evidenced by the infiltration of the subcutaneous tissues, and bronzing of the skin, resembling Addison's disease. The spleen, liver and lymphatic glands are enlarged, as well as the parotids on rare occasions; epileptiform convulsions may occur; other forms of the chronic type may be seen actually in adults.

The myxœdematous type is characterized by great thyroid insufficiency, scanty secretion of urine, dry skin, etc. These cases resemble classical myxœdema.

The cardiac type is characterized by cardiac arrhythmia. The frequent occurrence of extrasystoles produces a disturbance of the cardiac rhythm, which becomes especially marked on lying down; consequently the pulse is intermittent. A bradycardia of 24 beats per minute has been observed (Chagas). Pericarditis may supervene, and is usually fatal. The chronic cardiac disease may be the sequel to an acute infection in infancy or to repeated reinfections in later life.

The nervous type is characterized by "intention tremor," various paralyses, muscular contractions, and choreic movements. The brain and cranial nerves may be involved, producing various types of aphasia. Cerebral diplegias, ending in infantilism and mental deficiencies, have been described as a result of this disease.

It is only fair to state that not all authorities are agreed that the above description is distinctive of Chagas' disease. It has been pointed out, notably by Kraus, that it is difficult to distinguish endemic goitre and cretinism from the clinical picture of acute and chronic trypanosome infection as depicted by Chagas. According to Munk, in the district where Chagas made his discovery, 75 per cent. of the indigenous population have goitre, and a cretin is found in almost every family.

E. Reichenow (1934), who has studied this trypanosomiasis in Indian children and in half-castes in Guatemala, has remarked upon the absence of any distinctive features. Apparently it differs in intensity in different countries. In Guatemala there is no association with thyroid disease and only when the temperature is raised are the trypanosomes numerous in the blood-stream, and they are only found in thick-drop preparations. About 3 per cent. of children of 5 months of age were found infected. The trypanosomes were present in the blood for 10–30 days, when they disappeared of their own accord. No chronic stages of the disease were observed.

Diagnosis.—The trypanosome is usually present in very small numbers in the blood-stream, and prolonged search may be required for its detection. It may be necessary to collect the blood in citrated saline and subject it to prolonged centrifuging. The parasites may sometimes be found in the cerebro-spinal fluid by lumbar puncture; on the other hand, puncture of the lymphatic glands seldom

reveals them. A readier method of diagnosis consists in inoculating a guinea-pig with the patient's blood, when the developmental stages of the parasite may be found subsequently in the organs. In the acute form it is said that positive results are obtained by inoculation of guinea-pigs in 26 per cent. of cases. In chronic cases animal inoculation is negative. These difficulties in diagnosis have led to the elaboration of a complement-fixation test (Machado, Villela and Bicalho). The antigen is prepared from a glycerin extract of heart and spleen of infected animals. Lacoste, using a glycerin spleen extract of infected puppy, has recorded positive reactions in 68·5 per cent. (Machado reaction). The specificity of the test must be accepted with reserve as regards other forms of human trypanosomiasis, but it seems evident that there is no parallelism between the Machado and the Wassermann reactions.

Brumpt has suggested a method of xeno-diagnosis which consists in feeding laboratory-bred triatomas with the blood of the suspected person, when the cyclical development of the trypanosome can be readily demonstrated in the intestinal tract of the insect.

On clinical grounds, Chagas' disease is to be distinguished from endemic goitre, ancylostomiasis, Graves's disease, cretinism, myxœdema, Addison's disease, and other disturbances of the endocrine glands.

Treatment.—Unfortunately, arsenical and antimony compounds employed in the treatment of the other forms of trypanosomiasis have been found by no means so effective in Chagas' disease. Bayer 205 has no effect upon it at all. In the myxœdematous forms, thyroid medication should prove beneficial. Apparently spontaneous cure may occur in the febrile cases showing few symptoms; but originally C. Chagas did not consider this possible.

Prophylaxis.—This should be directed principally to the suppression of the insect concerned—*Panstrongylus* (*Triatoma*) *megistus* (Fig. 349). It is a large black insect belonging to the family Reduviidæ, well known to the natives, who call it "barbeiro," because, presumably, of its fondness for the face. The nymphs bite and can convey the infection, but the adults, having wings, are more dangerous. In the daytime they live in the grass walls and roofs of the dirty native houses, or of pigsties, coming out after dark in search of their food—blood. Their habits indicate better and cleanlier housing, sleeping off the ground, and protection by mosquito-netting.

The fact that the armadillo is the reservoir-host suggests that human habitations should be placed as far away from the burrows of these animals as possible, and that the floors of the houses should be constructed so that the armadillo cannot burrow underneath them. Brumpt has called attention to the fact that one form of reduviid, *Panstrongylus geniculatus*, which normally feeds on the armadillo, is commonly met with in the burrows of a Rock, or *Moco*, cavy, *Xerodon rupestris*, and that the trypanosome can be found in these bugs at

great distances from any human habitation. Spontaneous infection of local armadilloes and its presence in *Dasypus novemcinctus* have been reported. It is, therefore, possible that the disease exists independently of man. Robertson has also found large numbers of this trypanosome in the blood of an opossum (*Didelphis*) in Honduras.

ANIMAL RESERVOIR-HOSTS

The most important reservoir-host is the armadillo, which is distributed throughout South America and is frequently found in burrows in the vicinity of human habitations. In these situations, too, the bugs (*Panstrongylus geniculatus* and *P. megistus*) are at home. The long-tailed armadillo (*Dasypus novemcinctus*) is the commonest species, abounding in Guatemala up to altitudes of 5,000 feet. The "peludo" (*Euphractus sexcinctus*) is a much smaller animal, 18 in. in length. It is specially common in Brazil and feeds to a great extent on carrion. One other species of armadillo, *Cabassous unicinctus*, is also suspected. In addition to those mentioned Mazza, Miyara, Salomon and Sanjurgo have found the following to carry *T. cruzi* :—

EDENTATA :	*Euphractus vellerosus.*
	Zoedypus pichiy.
MARSUPIALA :	*Didelphis paraguayensis.*
	Lutreolina crassicaudata.
CHEIROPTERA :	*Nyctinomops macrotis.*
	Myotis levis.
CANIDÆ :	*Pseudalopex culpaeus.*
MUSTELIDÆ :	*Grisonella ratellina.*

CHAPTER V

LEISHMANIASIS

UNDER the title "Leishmaniasis" at least three diseases are included —Kala-azar, Oriental Sore, and Espundia. (Map III.) These, though clinically quite distinct and having each a definite topical and geographical distribution, are all associated with what, optically, at any rate, appears to be the same organism, *Leishmania*.

I. KALA-AZAR (VISCERAL LEISHMANIASIS)

Synonyms.—Tropical Splenomegaly; Black Sickness; Sirkari Disease; Sahib's Disease; Burdwan Fever; Dum-dum Fever; Ponos (Greece).

Definition.—An infective disease characterized by chronicity, irregular fever, enlargement of the spleen and often of the liver, and the presence in these and other organs of *Leishmania donovani*.

History.—The earliest description of this disease is by Clarke (1882), who stated that as far back as 1869 the attention of administrative officers in Assam had been directed to a peculiar disease called by the natives kala-azar, the ravages of which decimated, and in some instances almost depopulated, numerous districts in the Garo Hills.

Owing to the absence of malaria parasites, tertian or quartan periodicity, and the inefficacy of quinine in the cases of tropical splenomegaly which Manson had studied in England, he came to regard this disease as non-malarial and as one *sui generis*, and suggested in 1903 that it might be a trypanosome disease. In that year Leishman discovered certain small oval bodies in the spleen-pulp of a soldier who had died of "dum-dum" fever at Netley, and surmised these bodies to represent degenerative forms of a trypanosome. Later, Donovan in India corroborated Leishman's discovery. In December, 1903, Manson and Low found similar bodies in the spleen of a patient from India suffering from the same disease, and were able to show that these bodies were not endocorpuscular parasites. During the past two years kala-azar has been discovered in Brazil.

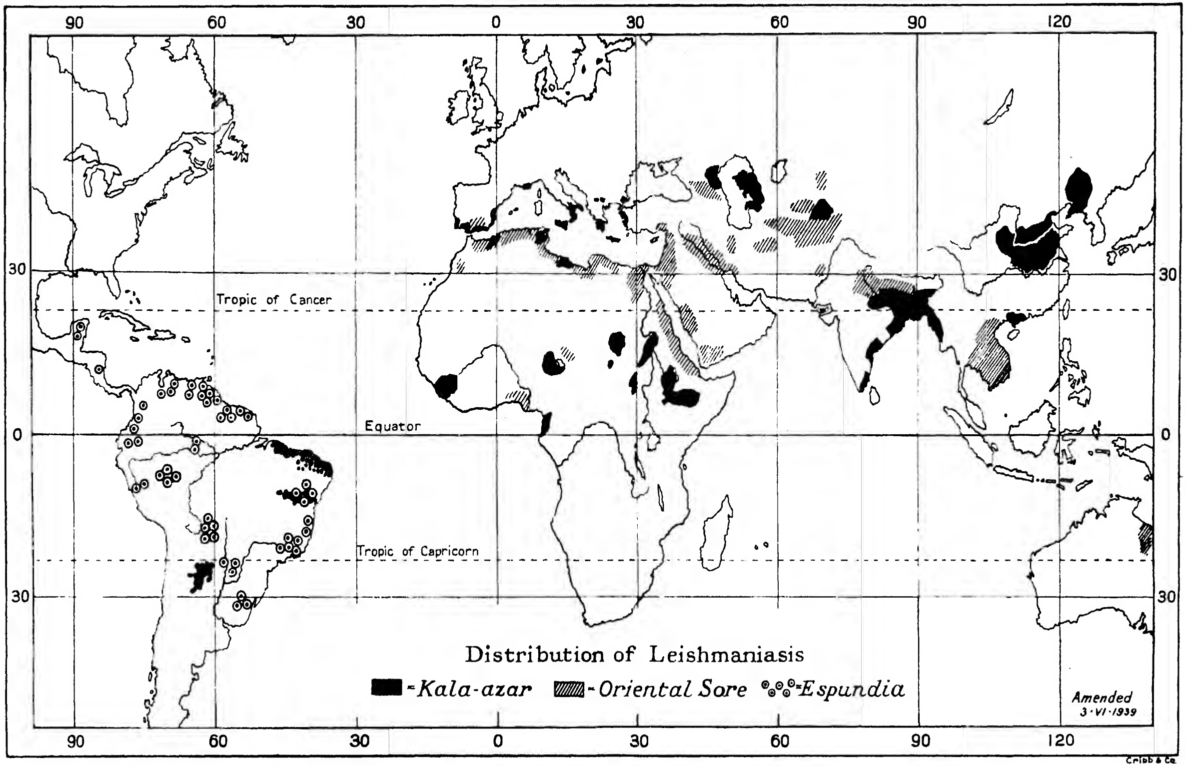
Geographical distribution.—Kala-azar is a widely distributed disease. It occurs in India, especially in Assam, Madras, and along the Ganges and Brahmaputra; in China, north of the Yangtse in a district between the coast and a line joining Peking, Hankow and, recently, as far south as Canton; in the Sudan (Kassala and Blue Nile districts), Western Abyssinia, Chad territory and Northern Kenya; in French Guinea; in Nigeria (Owen); in Tunis, Tripoli, Morocco,

Algeria, and (rarely) Egypt; in Sicily, Italy, Crete (Canea), Spain (in Madrid and the east and south coasts), Valencia (Lemierre), Turkey (Arar), Bulgaria (Mollow), Yugoslavia (Abramov), southern France (Marseilles), Portugal, Greece and the Grecian Archipelago (where the disease known as "ponos" has proved to be infantile kala-azar), Malta, Transjordania, and in Russia west and east of the Caspian, in Transcaucasia, and Turkestan, and it appears to be widespread in southern Manchuria.

The existence of kala-azar over a wide area in South America has been one of the surprising discoveries of recent years. Ever since 1911 veiled reference has been made to the probability of this disease existing on the Amazon and its tributaries. In 1913 Migone proved a case in Asuncion, the capital of Paraguay. More recently Romaña found cases in the Chaco in the northern Argentine. Up to 1934 these were regarded as curiosities till the existence of many others was found by the routine use of the *viscerotome* (*see* p. 370) in north-eastern Brazil: in a series of 47,000 examinations *Leishmania* have been found in 41. Up to the present E. Chagas has reported upon a series of 25 cases (*see* Map III), especially in Araca-jú in the state of Sergipe. The parasite, which differs in no morphological details from *Leishmania donovani*, or in other respects, cultural or pathological, has been provisionally named *L. chagasi*. It is said that differentiation can be established on serological and absorption tests in Noguchi's medium, but recently Adler has shown that there are no specific distinctions in this neotropical form which will infect hamsters. Its epidemiological resemblance to the Mediterranean form is shown by the discovery of infected dogs and one cat in the endemic focus around and to the south of Para. Ferreira and his colleagues have proved that the disease is transmitted by the sandfly, *P. intermedius*, and also, possibly, *P. longipalpis*.

It has been remarked by Kirk that the patchy distribution of kala-azar in the Sudan somewhat resembles that of Brazil. Here the disease is endemic in the Kassala and Fung districts bordering the Abyssinian and Eritrean frontiers. Hence the endemic area extends westwards as far as the White Nile. In the southern Sudan an endemic focus was found in the Kapoeta district, which lies between Abyssinia on the east and Kenya and Uganda on the south. A third endemic area exists in Darfur, the most westerly province of the Sudan.

Epidemiology.—Our knowledge of the epidemiology of kala-azar is gathered mainly from the Assam epidemic, which began about 1870, when the disease appears to have been introduced from Rangpur. Rogers believed it was originally introduced from Bengal, a theory supported by the names of "Sirkari disease" and "Sahib's disease" given by the Garos, who state that it was unknown among them until after the English took over their country. The epidemic advanced slowly along the valley of the Brahmaputra, taking seven years to spread less than a hundred miles. The introduction of the infection into a village was almost invariably traced to someone


90
60
30
0
30
60
90
120
Tropic of Cancer
Equator
Tropic of Capricorn
Distribution of Leishmaniasis
=Kala-azar
=Oriental Sore
=Espundia
Amended
3·VI·1939
Cribb & Co.

MAP III

coming with the disease on him from an infected locality, though some isolated localities escaped in a remarkable manner. Generally it clung to a place for about six years, and then disappeared without any apparent change in the local conditions. A house seemed to retain the infection for many months; the natives considered that it could not be reoccupied with safety under one year. During the course of the epidemic, kala-azar never extended far above the level of the Brahmaputra valley, the disease appearing first at the foot of the hills, and then spreading between them along the patches of low, flat, terai country. During the years 1922 and 1923 it extended up to the head-waters of that river into the Dibrugarh district, where it had never been known before. At present, kala-azar in India is confined to Assam, Bengal, Bihar and Orissa, and the United Provinces as far as Lucknow, and stretches in a patchy manner down the East Coast as far as Tuticorin. It has never spread to Ceylon. Kala-azar does not occur above an altitude of 4,000 feet.

On account of its deadliness, kala-azar, as it swept onwards, became a terror to the natives. Those suffering from the disease were turned out of the villages; sometimes they were made unconscious with drink, taken into the jungle and burnt to death. Some villages cut off all communication with neighbouring villages for fear of infection; other villagers deserted their homes and even migrated to a different district.

Napier has pointed out that the distribution of kala-azar in India is associated with one set of physical circumstances—the existence of alluvium and a certain heaviness of rainfall. In Assam there is a very definite house infection which in many cases is traceable to the introduction of a relative from a previously infected habitation, and there is reason to believe that, once introduced, kala-azar does not disappear until the whole of the population in the focus has been infected. It has been pointed out by McCombie Young that the epidemics of 1890–1900 and 1917–1929 were preceded by a devastating earthquake in one case, and by an even more devastating influenza epidemic in the other.

The neotropical form occurs in various types of country—in miserable hovels, in dense forests, in desert country and on river banks.

R. Archibald and Henderson have shown that kala-azar is found in particularly restricted areas in eastern Sudan, especially along the Blue Nile and its tributaries from the Abyssinian border to within 150 miles south of Khartoum; there the river flows through open, flat plains of thick loam, where the temperature rarely falls below 60° F.; there, too, the disease particularly attacks ill-fed children.

Giraud states that in the Marseilles district the disease has been apparent since 1922, 146 cases having been recorded. The endemic zone does not extend west of the Rhône in dry, scrubby districts where the "*fièvre boutonneuse*" is most abundant.

Although the foregoing are the only recorded examples of kala-azar as a widespread and active epidemic, it has been recognized that a disease clinically identical occurred sporadically in several places in India, the Mediterranean area, the Sudan, and China. Apparently, then, kala-azar occurs both as a sporadic and as an epidemic disease. In 1904, leishmaniasis was discovered in Tunis by Cathoire, and important studies by the Sergents, Nicolle, and many others have shown that the parasite occurs in many of the islands and countries in the

Mediterranean basin; that there it is practically confined to young children—infantile kala-azar—the parasite of which may be a distinct species; and, further, that, whilst in India dogs are never affected, in the Mediterranean basin and in Spain a large proportion of these animals are naturally the subjects of leishmaniasis (*L. caninum*), and in many cases are closely associated with the similar disease in children.

Adler and Theodor have emphasized the differences between Mediterranean and Indian kala-azar. In the Mediterranean, children under one year are attacked, while in India kala-azar in infants is a curiosity. There appears to be a definite and intimate connection between canine and infantile kala-azar; it is a seasonal disease both in infants and in dogs. The disease, which occurs on the outskirts of towns and villages, usually appears in April and is very rare after November.

Nicolle has differentiated the parasite, which is morphologically indistinguishable from *L. donovani*, as *Leishmania infantum;* in fact, Brumpt considers that this type is normally a parasite of the dog, and that it only attacks children accidentally. According to Hindle, Chinese hamsters inoculated with cultures of *L. infantum* exhibit a periarthritis of the limbs which is not induced by other species of leishmania.

In the Mediterranean area adults are not immune to infection, while in India children are more frequently attacked than was at first supposed. The close association of the canine and human disease in the Mediterranean area is far from being always observed: thus, dogs are commonly found infected in Morocco, while only recently has a single human case been seen there; and the same obtains in Marseilles. The canine disease also occurs in Dakar (Senegal) and in Teheran, where human kala-azar is unknown. Now C. U. Lee has discovered numerous infected dogs in Peiping and Andrews in Mukden (Manchuria).

The rate of infection of dogs with *Leishmania* is as follows: Tunis, 1·8 per cent.; Algiers, 7·1 per cent.; Lisbon, 3·7 per cent.; Athens, 13·75 per cent. Malta, 10 per cent.; Rome, 16 per cent.; Messina, 81 per cent.; Island of Hydra, 17 per cent. The disease occurs in dogs at any age, and the parasites, indistinguishable morphologically and culturally from *L. donovani*, are found in large numbers in bone-marrow, spleen, and liver. The aldehyde test has, on the whole, not been found so reliable as a means of recognizing the disease in dogs as in humans, though Sergent and Adler consider it of some value.

Schretzenmayr has described a sudden outbreak which occurred at the beginning of 1938 amongst Chinese troops in Canton, where the disease had not been previously noted. The first case was diagnosed through the discovery of leishmania in a malaria patient, and during the next five months a further 83 cases were identified. The disease appeared to follow the usual course, and in a number of cases jaundice was a feature.

Ætiology.—The kala-azar parasite (Plate VI) is now generally included by most authorities in the genus *Leishmania*, though some are disposed, on account of its life-history, to regard it as an *Herpetomonas*. We know two stages of this body, intracorporeal and extracorporeal. Possibly these represent respectively asexual and sexual forms; the former found only in man and in some other vertebrates, the latter obtained in artificial culture media and in the sandfly.

The distribution of the parasite within the body of man is very general. Apparently its special habitat is the endothelial cells of blood-vessels and lymphatics. It is particularly abundant in the spleen, in the liver, and in the bone-marrow (Plate VI).

The Leishman-Donovan body, as it is generally called, is a small ovoid or roundish organism measuring 2–4 μ in diameter. When stained according to Leishman's method it shows two lilac-coloured chromatin masses, one larger than the other, enclosed in a cytoplasm having a faint bluish tint about the periphery. The larger is known as the trophonucleus, the small rod-like body as the rhizoplast. The parasite divides by longitudinal fission.

The parasites, as they occur in man, are probably almost invariably intracellular. They grow and multiply within the host-cell, causing it to enlarge, and then, after disintegration of the nucleus, to disrupt. The parasites so set free either enter other endothelial cells or are taken up by the white blood-corpuscles, in which they are sometimes found in the peripheral circulation. In smear preparations they are often free or in clusters of various numbers, sometimes arranged with great regularity like the merozoites in the segmenting quartan or tertian malaria parasites. Sometimes as many as 50 to 200 parasites, or even more, are found together embedded in a structureless matrix or stroma, probably the remains of the original host-cell.

The parasite can be cultivated outside the body. The medium used by Rogers was citrated blood. When kept at blood-heat the parasites degenerate and disappear, but at a temperature of 20–22° C. they multiply rapidly and assume an elongated motile flagellated form. The flagellum arises from the rhizoplast and projects at the anterior end of the body as in *Herpetomonas*, but there is no undulating membrane as in the trypanosomes. These flagellated forms measure 12–20 μ in length, and multiply by longitudinal fission. They move actively, flagellum foremost, and tend to agglomerate into rosette groups with their flagella directed centrally. The N.N.N. medium (p. 1037) is now considered the best for culture of this organism, but technique must be particularly observed, as bacteriological contamination rapidly kills the parasites. Wenyon has succeeded in keeping the parasite alive in successive cultures over a period of fifteen years. The flagellated form has not been found in the human body, but Wenyon has noted that these forms may occur associated with typical leishman bodies in canine leishmaniasis. The parasite can be communicated to dogs, cats, jackals, monkeys, rats, voles, hamsters, and mice, provided that large doses of the virus are injected into the peritoneal cavity or into the liver. To infect a dog, it is necessary

to inject 2–4 c.c. of a thick emulsion of infected spleen, liver, or bone-marrow. Intravenous injection is by no means so successful, while injections of cultures rarely succeed.

Lwoff has now shown that for growth *Leishmania donovani* and *L. tropica*, like *Trypanosoma cruzi*, require ascorbic acid, hæmatin and also an unknown substance in the serum. Archetti has shown that Reichenow's medium of citrated blood and Ringer's solution, normally used in the cultivation of trypanosomes, is very suitable for the growth of leishmania.

Transmission of the parasite.—It was formerly thought, from the close association of the human and canine disease in the Mediterranean area, that the dog constituted the chief reservoir of infection, but the association is not now so complete as to be conclusive for certain areas, as, for instance, in Iran, where kala-azar in dogs is common, while human kala-azar is absent. In China, a small rodent, the striped hamster (*Cricetulus griseus*), has proved in the laboratory to be extraordinarily susceptible to infection, and this animal has once been found to be naturally infected in the wild state. These are the facts which are known, but they do not at present afford by any means a sure explanation of the peculiar geographical distribution of kala-azar on the grounds that some wild animal is the reservoir of infection to man.

On account of the peculiar topographical distribution of kala-azar in India, Sinton first suggested in 1922[1] that a sandfly (*Phlebotomus*) was the insect vector, and in the same year Napier found a close correspondence between the distribution of *P. argentipes* and the number of kala-azar cases. It was further found that this species of sandfly feeds solely on man. A similar suggestion as regards the leishmania of oriental sore had already been put forward by Wenyon in 1911 and subsequently proved correct by the Sergents in Algiers. Since that time a large amount of work on the subject has been performed by Christophers, Shortt, Knowles, Napier, Barraud, Lloyd, and Smith, with the result that a very rapid, intensive and remarkable development of herpetomonas forms was found to occur in one species of sandfly—*Phlebotomus argentipes* when fed on the blood of patients suffering from kala-azar. The whole midgut becomes infected and in some individual insects the infection spreads to the pharynx, and even to the buccal cavity (Fig. 23). The distribution of this species of *Phlebotomus* in India corresponds closely to the distribution of kala-azar; in other endemic areas a different species of *Phlebotomus* is involved, as in China, *P. major* and *P. sergenti* (Hindle), and in the Sudan *Phlebotomus perniciosus* var. *langeroni*. One of the main difficulties encountered in these experiments is the delicacy of these small insects and the trouble experienced in keeping them alive longer than five days after feeding. The crucial test, the actual transmission of kala-azar to man under experimental conditions, still remains to be performed, and though hamsters have been infected by injection of crushed sandflies, only one animal out of many thousands of experiments has so far been successfully infected by sandfly bite.[2] The members of the Kala-azar Commission undertook an experiment with seven volunteers and a large number

[1] This was in a private communication to Knowles.

[2] For possible explanation of this, *see* concluding sentence.

of infected sandflies. The result was negative. The conclusions of the Indian Kala-azar Commission which closed its labours in 1930 ended in a note of despair. The experiments on sandflies extended over a year, and

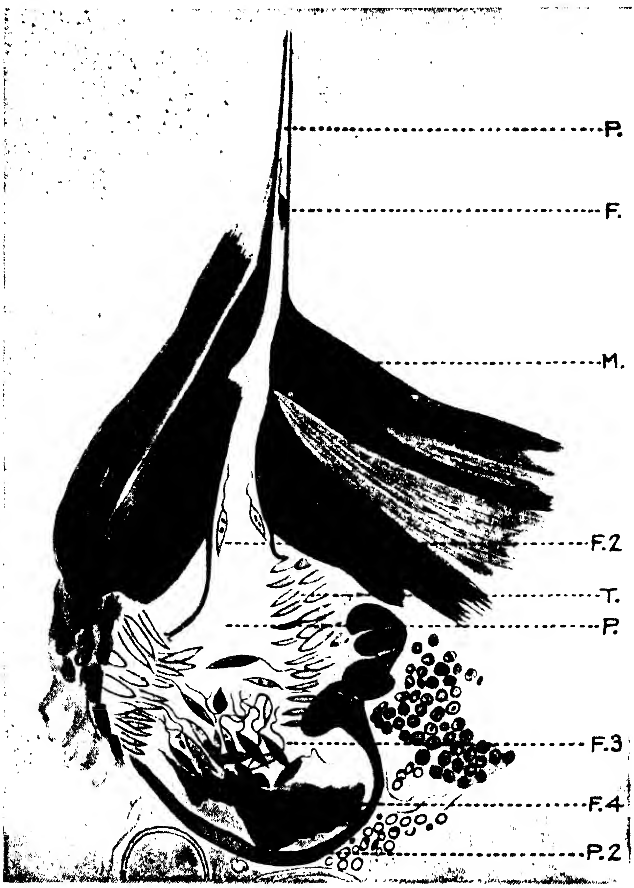


Fig. 23.—Section of ***Phlebotomus argentipes*****, showing pharyngeal infection with** ***Leishmania donovani*****.** *(From Indian Jl. Med. Res.)*

P, lumen of pharynx; P2, posterior termination of pharynx; T, ridges of crinkly portion of pharynx; M, muscles of pharynx; F, flagellate near anterior extremity of pharynx; F2, flagellates anterior to crinkly portion; F3, flagellates breaking free from main mass of growth; F4, massive growth of flagellates at posterior end of pharynx.

during that period 273,467 sandflies were bred out, and of these 79,939 were fed in the laboratory; but now (1935) Smith has shown that, in the hamster, the disease takes 18 months to develop after the animal has been bitten by an infected sandfly.

Wu and Sun in China (Tsingkiangpu) have subjected local species of sandfly to experimental infection after feeding on kala-azar patients and infected hamsters. The infective rates were :

19·26 per cent. from kala-azar patients, 56·25 per cent. from hamsters—in the species *Phlebotomus chinensis ;*

1·17 per cent. from kala-azar patients, 32·68 per cent. from hamsters—in the species *Phlebotomus sergenti* var. *mongolicus.*

Shortt, Barraud and Craighead have reported the occurrence of naturally-infected sandflies in a kala-azar house.

Formerly it was held, mainly by Patton, that the bed-bug was the most probable insect vector, but the work of Mackie (1915) and Cornwall (1916) greatly weakened these arguments.

An account of the bionomics of the sandfly will be found on p. 997.

In Malta, according to Adler and Theodor, 10 per cent. of native dogs are naturally infected, especially in the summer months. The majority of the infected dogs are mangy and emaciated, though some may look healthy. Seborrhœa and depilation are the most frequent signs. The skin condition is due to infiltration of the macrophages round hair follicles, and may be present with only slight visceral infection.

In Catania (Sicily) and in Malta, Adler and Theodor believe that both the infantile and the canine parasite of kala-azar are transmitted by *Phlebotomus perniciosus.* The distribution of the disease in Sicily and in Malta is said to be very local and no sandflies are found where there is no disease. The sandflies could be infected by feeding them on the unbroken skin of infected dogs. These same workers predicted that sandflies of the *major* group, the members of which are, as far as it is known, responsible for the transmission of kala-azar, would be found in the indigenous areas in the Sudan. *Phlebotomus langeroni* has now been found there by Sir Robert Archibald.

The Chinese hamster (*Cricetulus griseus*) is a small species of the size of a field-mouse, 12 cm. in length and 30 grm. in weight. Common round Peking, it extends into Chinese Mongolia. It makes extensive burrows, frequenting cornfields and destroying quantities of grain. It is greyish-brown in colour, pale beneath, with a decided median dorsal stripe, and has a short, stumpy tail.

The marmot of Greece and Palestine (*Cricetulus auratus*) has also been found susceptible by Blanc and Caminopetros, and also the Macedonian spermophile (*Citillus citillus*)

Khaw, in China, has found that the mole rat (*Myospalax fontanieri*) and the ground squirrel (*Citillus dauricus*) are susceptible to leishmania infection. The former is as easily infected as the hamster, the latter less so. The following species of hamster also have been infected : *Cricetus triton*, *C. accedua*, and the common hamster, *C. frumentarius* (Mayer, 1926). In the Sudan, Archibald (1914) found that gerbilles (*Gerbillus pyargus*) and jerboas (*Jaculus gordoni*) could be infected in the laboratory. Da Cunha has reported the successful infection, with the leishmania (*L. chagasi*) of South American kala-azar, of the hamster, the rhesus monkey, and the dog.

Hu and Cash have made the most interesting observation that the leishman bodies are taken up by the cells of the reticulo-endothelial

system, or clasmatocytes, and, in experimentally-infected hamsters, become massed as a thick layer of heavily infected tissue lying immediately underneath the skin, though externally no change can be seen on the surface of the body. This observation has been confirmed by Hindle. In skin sections from a fatal case of kala-azar a similar condition was seen. All levels of the skin below the epidermis contained leishmania-filled cells collected in large masses about the sweat-glands and arterioles and scattered diffusely throughout the corium. The relationship between this condition and the curious skin eruptions (p. 187) described in India is of interest, and it suggests the possibility of the manner in which the parasites are abstracted by blood-sucking insects when scanty in the peripheral blood.

Suggestions have been made that the transmission may be direct from man to man through the fæces. The evidence for this appears to be based upon the fact that leishmania parasites occur in polypoid masses in some intestinal cases, and that leishmania-like bodies have been found in the intestinal mucosa in kala-azar cases by Mackie, Knowles and others. In addition, Shortt and his colleagues have demonstrated the presence of Leishman-Donovan bodies in numbers in blood-and-mucus stools in a boy suffering from kala-azar with dysenteric symptoms, and further they have shown that hamsters kept close together in a small cage contracted the infection from one another in the absence of an insect intermediary.

Nasal and oral secretions.— Forkner and Zia in China have discovered leishmania in the material obtained by passing an ordinary swab over the nasal mucosa of nine kala-azar patients, and parasites were also seen in the material blown from the nose (droplet infection). The tonsils were found to be heavily infected. Material from these situations have produced kala-azar in hamsters by intraperitoneal inoculation. Apparently it is not necessary for the organism to pass through the flagellated stage in order to render it transmissible.

Shortt and Swaminath have reported finding *Leishmania donovani* in the nasal mucus from cases of Indian kala-azar. In a certain proportion of advanced cases viable parasites are also excreted in the urine.

That kala-azar may occasionally be a *congenital infection* has been shown by Carmichael Low and Cooke (1926), who proved that the disease developed in a child seven months old, born in England of a mother who suffered severely from kala-azar during pregnancy, but it has been pointed out by Forkner that infection of the child from the nasal mucus of its mother might be a possible explanation.

Predisposing causes.—Kala-azar attacks both sexes and all ages, but shows a predilection for the recently arrived immigrant in preference to the residents of the endemic district. In the Mediterranean basin it occurs almost, though not quite, exclusively in children (five months and upwards): in India it occurs at any age.

Pathology.—The spleen is greatly enlarged, and the thickened capsule may show signs of perisplenitis. The trabeculæ are enlarged; the pulp is increased in bulk and full of blood. A section or smear

preparation, appropriately stained, will show prodigious growth in the large mononuclear cells. The liver also is generally much enlarged, and is brown or mottled on section. The parasites are in great abundance, occupying large mononuclear cells, attached or free, in the dilated hepatic and portal capillaries throughout the reticulo-endothelial system. Christophers has shown that primarily the parasites are engulfed in macrophage cells of the blood-vessels, while Hu and Cash have shown that in artificially infected animals a true blocking of the endothelial system takes place. There may be some cirrhotic changes, but the hepatic cells, though atrophied and perhaps fatty, never contain parasites. The bone-marrow is similarly packed with parasite-laden cells. Intestinal ulceration is very common, and parasites may be found in the walls of the ulcers, as well as in skin ulcerations and in the lymphatic glands. Occasionally they are found in connection with the blood-vessels in the kidneys, but never in the epithelium of the secreting tubules. Shortt and others have succeeded in cultivating the parasite from the urine in three cases.

The distribution in the body has been explained by Laveran on the assumption that the parasites are taken up by the endothelial cells, when they multiply till the cell ruptures and the organisms escape into the blood.

Symptoms. — The *incubation period* is difficult to fix. In the case of one Englishman under Manson's care, the time that elapsed from his arrival in perfect health in the endemic region and the onset of the fever which terminated in kala-azar (diagnosed microscopically both before and after death) was under ten days. Kirk, on the other hand, from accurate observations

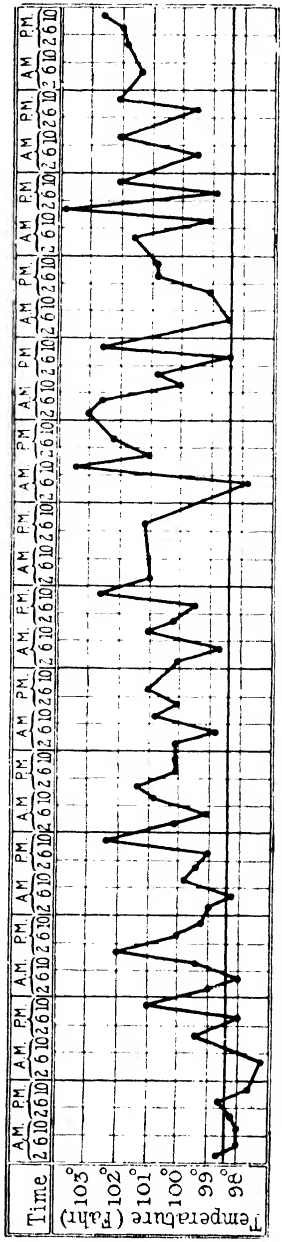


Chart 6.—Four-hourly chart of kala-azar, illustrating the "double rise" in the twenty-four hours. (*Orig.*)

in the Sudan, fixes the period between three and six months. In a proportion of instances, as in some artificially-infected dogs, the disease, like dermal leishmaniasis, may remain latent for months. In advanced cases in man the parasites may disappear from the tissues before death.

The onset of the disease may be either gradual or sudden ; in the former instance it cannot be diagnosed at all on clinical grounds. In the latter there is usually high fever, which may be preceded by rigor and, in some cases, by vomiting. The initial fever—intermittent in some instances, more frequently remittent, often with a double re-

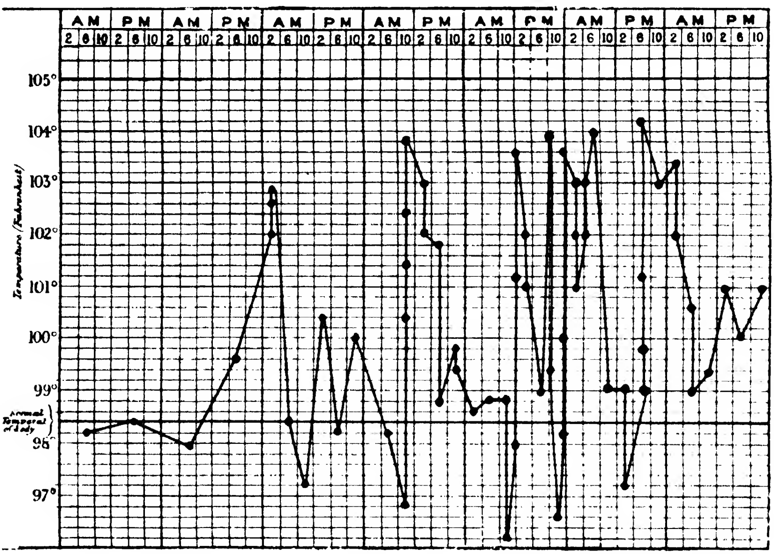


Chart 7.—Temperature chart of acute kala-azar, showing "double crisis."
(*Dr. G. Carmichael Low.*)

mission in the twenty-four hours, resembling that of subtertian malaria —may be very severe (Charts 6, 7). It lasts from two to six weeks, occasionally longer. Waves of fever separated by apyrexial periods may often simulate undulant fever, and during the pyrexial periods both the liver and the spleen enlarge. There may be daily rigors, so that malaria may be suspected. A four-hourly temperature chart in a well-marked case may show a double or even a triple rise of fever.

The spleen is usually enlarged from the commencement of the illness, whilst the liver does not become appreciably bigger till the disease has lasted some months. In China, and in Brazil, a uniform painless enlargement of the cervical lymph-glands has been observed.

Then comes a period of apyrexia and general improvement, to be

followed once more by fever and splenic and hepatic enlargement, and perhaps tenderness. In women amenorrhœa is often an early symptom. In this way spells of fever and apyrexia recur for months, absolutely unchecked by quinine, until finally a low form of fever, rarely over 102° F., becomes more or less persistent. Profuse sweats are common during remissions at all stages of the fever; rigors occur exceptionally. Pains in the limbs often suggest rheumatism. When the disease is thoroughly established, emaciation and anæmia become noticeable, and, together with the enlargement of the liver and spleen, cause the patient to present a typical appearance. Œdema of the legs, sometimes circumscribed œdemas, or even ascites may now be present. In many cases the skin acquires a strange earthy-grey colour; this dusky pigmentation, which has given rise to the native name, kala-azar, "the black disease," is best seen on the feet, hands and abdomen in Europeans, though very difficult to distinguish in dark-skinned natives. The hair is apt to become dull, dry, and brittle, and may fall out; petechiæ, in the axillæ especially, are not unusual; epistaxis and bleeding from the gums are common. This condition of chronic fever, enlargement of spleen and liver, emaciation, and anæmia (Fig. 24) may continue for months, or even one or two years, until improvement sets in, or more usually—96 per cent. of cases (Rogers), 150 recoveries in 2,000 cases (Price), 24 in 100 cases (Lignos)—until the patient is cut off by an intercurrent disease, especially dysentery (90 per cent.). Broc has pointed out that marked enlargement of the spleen is not necessarily an outstanding feature, and the Editor has even watched the development of typical kala-azar in patients in whom enlargement of the liver was at first the only sign.

Fig. 24. -Kala-azar in Indian boy. (*Dr. L. E. Napier.*)

The outstanding clinical feature is that, in spite of the patient's weak and emaciated condition, the pyrexia, and the protuberant abdomen due to splenic enlargement, he preserves a good appetite and a clean tongue, while with a temperature of 102° F. he may be working quite unaware that he has fever (Fig. 24). There is an absence of malaise and apathy. In this respect kala-azar differs from malaria and other toxic fevers, such as typhoid. Kala-azar usually lasts several years, but the Sudan cases, especially, may run an acute course, the disease lasting about five months.

The number of red corpuscles is not infrequently over 4,000,000, and, as a rule, over 2,500,000 even in advanced cases.

The most remarkable change seen in the blood is the great and constant reduction in the number of leucocytes (*leucopenia*). Instead of there being 1 white to about 625 red, as in a normal subject, the proportion is commonly from 1 : 2000 to 1 : 4000, and may be lower still. The reduction is most marked in the polymorphonuclears ; the lymphocytes and large mononuclear leucocytes, although greatly reduced in number, usually show a relatively increased percentage, and it is this reduction of the leucocytes to 3000 or even 1000 per cu. mm. which renders these patients specially liable to pneumonia and septic infections. The condition known as acute *agranulocytosis* is produced in some cases, as described by Forkner and Zia in China, Shortt and Swaminath in India and by Gritti in Italy. The blood-pressure is generally low, the systolic reading being below 100 mm. of mercury. Hæmic murmurs of the heart are noted. Hæmorrhages may occur from any part of the body, and purpuric patches may appear on the skin after local injury. Death may ensue from several causes. When due to the disease alone it results from exhaustion. Dysenteric symptoms are frequent, and may be due to intestinal lesions caused by Leishman-Donovan bodies, or to a superadded infection with amœbic or bacillary dysentery. Broncho-pneumonia and cancrum oris are frequent terminal symptoms. Proctor, however, reports that the latter complication can be arrested in the early stages by scrupulous daily inspection of the mouth. Should a grey line of ulceration on the gums be seen, it should be energetically treated with carbolic acid and spirit. It may be that this gangrenous process is not so much due to the kala-azar as to the leucopenia which accompanies it, and it has a striking analogy in the angina which is so characteristic of agranulocytosis.

Infantile kala-azar.- The symptoms of the infantile form are, on the whole, similar to those of the adult type and differ only to the extent that might be expected in a disease occurring in very young children. The onset is usually insidious, with some fever and gastro-intestinal upset. The spleen enlarges and the child becomes apathetic and anæmic and emaciated. Irregular attacks of fever occur and the child often suffers from epistaxis, bleeding from the gums, and hæmorrhages into the skin. The lymphatic glands are usually enlarged.

Dermal leishmanoid.—A cutaneous form of leishmaniasis, in which the parasites occur in nodules of the skin, was apparently first reported by Thomson and Balfour in the Sudan in 1909 and has since been observed in the Blue Nile (Kassala) districts. It was recognized by Brahmachari in India and described under the name of dermal leishmanoid, or post-kala-azar leishmaniasis. It is certainly a sequel to generalized infection with *L. donovani*, as more than half the patients who exhibit this curious eruption have suffered from kala-azar about

one year previously, and have received antimony treatment for this disease. The *Leishmania* are found in smears from the nodules, and cultures have been obtained from the lesions. It is not at all clear at present what the significance of this phenomenon is, or what factor causes the organisms to establish themselves in the skin. This condition occurs in all classes of the community and in persons of all ages and both sexes. Though not all give a history of having suffered from kala-azar, it is generally conceded that leishmanoid is a sequela of generalized leishmania infection, and the dermal lesions usually make their appearance from one to two years after all signs of visceral infection have disappeared. The *xanthoma* stage would appear to be the final outcome of the condition, but it is rarely seen, and then in cases giving a history lasting 10–30 years.

The first or depigmented stage usually appears as depigmented patches on the face and upper extremities, gradually spreading to the remainder of the body. Minute dots gradually enlarge till they become irregular areas half an inch in diameter, which occasionally tend to break down. There is found œdema of the subpapillary tissues accompanied by dilatation of the vessels. Below this there is infiltration by macrophages in the region of the subpapillary plexus. The second, or nodular stage, is seen about two years after kala-azar treatment. Usually the nodules replace the depigmented patches, but there are certain areas, such as the face, where the nodules appear much earlier than in other parts of the body. The nodular lesions may extend to the mucous membranes and may closely resemble leprosy. The epithelium is thin and the subpapillary layer is œdematous, with atrophy of the fibrous and elastic tissue. Subjacent to this œdematous area is a granulomatous mass consisting of proliferating macrophages. There is an xanthomatous form, known as *Xanthoma type*, which is quite unmistakable, and in which the parasites have been found in the peripheral blood in two cases (Fig. 25). The lesions are raised, orange-coloured plaques which are painless and do not ulcerate.

Preliminary treatment with massive doses of potassium iodide cause the nodules to ulcerate and they become susceptible to intravenous injection of aminostiburea (*see* p. 194) of which a total of 5 grm. is necessary (Napier). Some cases are, however, entirely resistant to it. Inunction with metallic antimony is said to assist (Brahmachari).

Eye lesions.—R. E. Wright has shown that eye lesions in kala-azar, as in malaria, are due to retinal hæmorrhages in the posterior segment of the eye.

Diagnosis of kala-azar.—Irregular chronic fever with enlargement of the spleen and a diminution in the number of leucocytes in patients from the endemic zone suggests kala-azar. An examination of the blood can at once exclude leucocythæmia and, if taken together with absence of tertian or quartan periodicity and the inefficacy of

quinine, malaria. Differential diagnosis from typhoid and malignant endocarditis and Egyptian splenomegaly (*Bilharzia mansoni*) should present no special difficulties, but that between trypanosomiasis and kala-azar may be difficult, and unless their respective parasites are detected a positive diagnosis is impossible, although geographical considerations, the rash, and lymphatic enlargements may assist.

Fig. 25.—Dermal leishmanoid. Extensive nodular lesions on face.
(*Acton and Napier, Ind. Jl. Med. Res.*)

Splenic puncture must not be lightly undertaken. A preliminary examination of the blood should always be made, not only with a view to ascertaining the presence of the leishman body, but to exclude leucocythæmia and obviate the necessity for splenic puncture, and the attendant risk of fatal hæmorrhage so easily induced in that disease. When the liver is enlarged, it should be selected, as a less vascular organ and less easily torn, for puncture, but, as a general rule, the parasites are not so abundant in this organ as in the spleen. In performing puncture, the abdomen had better be fixed firmly with a binder to prevent, as far as possible, movement of the diaphragm and con-

sequent risk of tearing the punctured organ. The patient should be injected with $\frac{1}{100}$ gr. of atropine one hour previously, and the puncture site infiltrated with novocain to deaden pain. The administration of 30 gr. of calcium lactate the evening before and on the morning of the puncture, and the fixation of the lower border of the spleen are advocated. A hypodermic needle, scrupulously clean and dry,[1] and connected with the barrel of the syringe by a short length of rubber tubing, should be used, the patient being directed not to start or breathe when the puncture is being made. The type of needle is most important. The bore should be neither too big nor too small. The Editor has found Maw's size No. 10, with a shaft 40 mm. in length, the most suitable, and Napier has devised a special spleen-puncture syringe (Fig. 26). Failure to draw blood is not to be regarded as failure to obtain material for microscopical examination; on the contrary, it is an advantage, as the object is to procure spleen or liver pulp, not blood. After

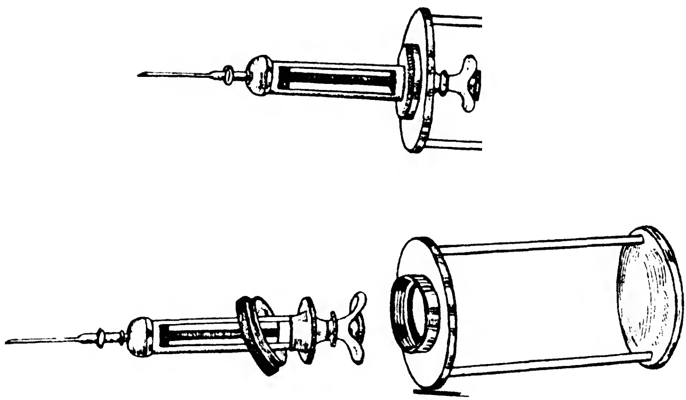


Fig. 26.—Spleen puncturing syringe. (*After Dr. L. E. Napier.*)

the contents of the needle have been blown out on a slide, it may be trans-illuminated by an electric pocket-torch to discover the minute sago-like masses of splenic tissue. A film should then be spread and, after it has dried, stained by Leishman's or Giemsa's method, and then examined with a $\frac{1}{12}$ in. objective. The parasite is easily recognized by its size, shape, and two chromatin masses. The recent discovery of leishman bodies in the sub-cutaneous tissues suggests that removal of a piece of skin may be a safe and rapid method of forming a diagnosis in kala-azar, as well as in the allied condition, leishmanoid.

Giraud and Gaubert point out the dangers of spleen puncture, especially in the case of infants. A child of six died from intraperitoneal hæmorrhage from a laceration, 3 mm. in length, of the spleen capsule.

Napier has now (1936) reported the results of 5,000 splenic punctures without a death. He gives 30 gr. of calcium lactate the night before, a second dose in the morning, and a third immediately after the puncture. The patient is confined to bed for the whole day, and is given a cup of tea

[1] The presence of a trace of water in the needle will distort or burst the parasite and render it unrecognizable.

at 6 a.m., but no food until one hour after the operation, usually at 11 a.m. A light binder is tightly applied round the abdomen. The operator sits on the bed on the left of the patient, facing him. The advantage of the spleen-puncture syringe is that it can be used with one hand, leaving the other free to locate the spleen (Fig. 26).

Sternal puncture.—Lovando states that in Athens sternal puncture is simpler, safer and surer as a method of diagnosis than spleen puncture, and Giraud considers tibial puncture, which can be carried out without a local anæsthetic, the method of election in the case of young children. The point selected is the outer face of the tibial epiphysis, 1 cm. below the knee-joint. A fine trocar and cannula is passed till entry into the spongy tissue is felt by the sudden loss of resistance.

Chung (1938) states that he has used sternal puncture as a means of diagnosis in Peiping for the last two years and is convinced that it is the best method of diagnosing kala-azar in hospitals and rural stations. A local anæsthetic is seldom necessary, save for nervous individuals, and a shortened lumbar-puncture needle can be employed. It is inserted in the mid-line at an angle of 30 or 40 degrees at the level of the upper half of the second or third interspace. The needle, with contained stylet, is pushed with a boring action through the bony lamina. When the marrow cavity is reached, the stylet is removed and a syringe for aspiration attached to the needle.

D'Oelsnitz finds that the most reliable indication of the early stage of infection is the discovery of the parasite by sternal puncture and the increased density of the serum under the influence of the organic antimony compounds, as judged by photometric methods. The actual procedure is to add to a 1 : 1000 dilution of serum a 1 : 100 solution of urea stibamine. A density of 0 to 4 for normal individuals is replaced by one of 8 to 30 for kala-azar cases.

The frequency with which this parasite appears in the blood has been a matter of much discussion. Undoubtedly, in some places, as in Madras and Assam, it occurs in about 60 per cent. of all cases examined, and therefore the diagnosis may be made by simple blood examination; but this is by no means the case in other parts of the world.

Knowles and Das Gupta employed thick films prepared by placing four drops of blood on a clean slide, mixed so as to cover an area of ½ sq. in. The film is covered with a Petri dish, and dried at 37° C. for two hours. It is then flooded with glacial acetic acid (2·5-per-cent.) 4 parts, crystalline tartaric acid (2-per-cent.) 1 part. The action should be complete in five to ten minutes. After tilting off the fluid, the film should be fixed with methyl alcohol and stained with dilute Giemsa. By this method the parasites may be found, enclosed in leucocytes, in 67 per cent. of kala-azar cases.

A less elaborate technique is employed by Shortt and his colleagues. A small drop of blood is placed at one end of a slide and a second one applied in the usual manner and pushed till the blood is almost exhausted. At this point it is abruptly lifted off, with the result that the blood-smear ends in a straight edge which is somewhat thicker than the rest of the smear, and in this the parasites can be demonstrated within the leucocytes.

By centrifuging 5 c.c. of blood diluted in Locke's solution (modified) (sodium chloride 9 grm., potassium chloride 0·4 grm., calcium chloride

0·2 grm., sodium citrate 10 grm., distilled water 1,000 c.c.), at a speed of 750 revolutions, Young and van Sant state that parasites are readily discovered in films made from the bottom of the centrifuge-tube. It is stated that the parasites appear in the blood-stream after injection of 10–20 min. of a 1 : 1000 solution of adrenalin. Chopra has found that intravenous injection of pentavalent antimony preparations cause a rhythmical contraction of the spleen and the appearance of the parasite in the peripheral blood. According to Wenyon and others, the presence of the parasite in the peripheral blood can best be demonstrated by blood-culture. For this purpose 2 c.c. of blood should be drawn off by means of a 2-c.c. Record syringe and mixed with 1 c.c. of 6-per-cent. citrate solution in a sterile tube, which should be placed in a cool incubator and allowed to sediment for two hours. The deposit at the bottom of the citrate solution is then drawn up by means of a pipette, inoculated into two or more tubes of N.N.N. medium, and again placed in a cool incubator. Examination of the cultures should be made about the tenth day, when flagellate forms may be observed, but it is not wise to discard the tube as negative until at least twenty days of incubation have elapsed. Spleen pulp may also be cultured in the same manner.

Biochemical reactions.—There appears to be little evidence for the statement that the serum of kala-azar cases gives a positive Wassermann reaction. The alkalinity of the blood is said to be decreased, while in some cases the coagulation-time is very considerably prolonged.

Aldehyde test (or the serum-formalin reaction) (*Napier*).—This test has proved to be very useful as a method of diagnosing kala-azar on a large scale among gangs of coolies where systematic splenic puncture is obviously impracticable. For this purpose about 5 c.c. of blood is withdrawn from a vein and allowed to stand a sufficient time for the serum to separate ; 1 c.c. of *clear* serum is then placed in a test-tube (3 by ½ in.), and to this 1 drop of 30-per-cent. formaldehyde, or commercial formalin, is added. The serum is at once well shaken and placed in a test-tube rack at room-temperature. In a certain proportion of cases of kala-azar, especially in chronic cases, solidification of the serum takes place within a space of three to twenty minutes, but a control of normal serum should always be made. Napier himself states that "jellification" with opacity (like the white of an egg) of the serum may be taken as diagnostic of kala-azar if the disease is of three or four months' standing, but milkiness of the serum without solidification only takes place in early cases of the infection. Should the serum be hæmoglobin-stained, this will change to chocolate-brown after twenty-four hours. In certain cases of syphilis, leprosy, phthisis, and malaria the serum will solidify, but remains clear and does not become opalescent as in kala-azar. The reaction, which occurs in twenty minutes, is given as +++ ; after two hours as ++, and after twenty-four hours as +.

In kala-azar it has been proved that the plasma globulins are increased, while the albumins are diminished. In kala-azar, the albumins are 2·8 ; the globulins 4·0, as compared to 4·5 and 2·0 per cent. respectively in the normal. Lloyd and Powell have constructed a typical globulin curve of kala-azar in which euglobulin constitutes 40–50 per cent. of the total globulin. Auto-agglutination of the red blood-corpuscles is often noted as in trypanosomiasis, more especially in advanced cases.

Antimony test.—Chopra has pointed out, and Napier has confirmed, the curious fact that the addition of a 4-per-cent. solution of pentavalent antimony compounds to kala-azar serum causes a heavy precipitate, the amount of which corresponds to the efficacy of that compound in the treatment of the disease.

The method is as follows: One to two drops of blood from the pricked finger are allowed to flow into a Dreyer's tube in which has been placed 0·25 c.c. of a 2-per-cent. potassium acetate solution. The tube is then inverted to mix the contents; a little of this mixture is transferred to another tube, and a 4-per-cent. solution of the antimony compound (Stiburea, for example) is added by means of a capillary pipette and allowed to percolate along the wall, so that it comes to lie below the blood mixture. In a positive case a flocculent precipitate forms at the junction. In very early cases it may not appear for 10–15 minutes: in more advanced ones it is immediate. The character of the precipitate is important in kala-azar: it is so flocculent that it is not easily broken up by shaking and it does not disappear in twenty-four hours.

In cases of doubt it is a good procedure to dilute the serum with 10 volumes of distilled water and to repeat the test. It is necessary that alcohol should not be used for cleansing the finger. André (1932) claims that the results are improved by reading the opalescence produced in kala-azar serum by urea stibamine by means of the " Vernes-Bricq-Yvon " photometer.

Napier has stated that the aldehyde and antimony tests are almost of equal value. Out of 201 cases of kala-azar diagnosed by discovery of the parasite, 156 gave a positive antimony test, and 128 the aldehyde test.

Caminopetros' test consists of adding the serum to be tested, drop by drop, to a 2-per-cent. solution of sulphur in distilled water, when a turbidity develops which persists.

In the Chinese form of the disease, in which enlargement of the lymphatic glands occurs, diagnosis may be made by gland puncture or excision.

The **differential diagnosis** has to be made from splenic anæmia, Banti's disease, and Egyptian splenomegaly (*Bilharzia mansoni*), which, save for the absence of the parasite and the characteristic pyrexia, may closely simulate kala-azar. Visceral syphilis with enlargement of liver and spleen may have to be excluded. The same may be said of malignant disease and tuberculosis of the spleen. In China and Japan kala-azar may have to be differentiated from intestinal bilharziasis (*Bilharzia japonica*), in which enlargement of the abdominal organs may occur. The remarkably clean tongue and the good appetite serve in some measure to differentiate kala-azar from chronic malaria, to which may be added the considerable emaciation, the absence of extreme anæmia, the double daily rise of temperature (in 88 per cent. of cases), pistension of the superficial abdominal veins, and pigmentation of the extremities.

Treatment

Antimony treatment.—From 1912 onwards it has been known that in antimony and its compounds we possess a specific for the treatment of kala-azar. At first intravenous antimony tartrate (*sodium-antimony tartrate*) or

less commonly, potassium antimony tartrate, was employed by the method introduced by Vianna in Brazil for dermal leishmaniasis. The results achieved in India by Rogers, Mackie and others were very encouraging, and subsequently led to the development of more highly organized compounds of antimony, such as the pentavalent salts.

The reaction of a kala-azar patient to antimony treatment can be assessed in various ways ; for instance, in the improvement in the clinical condition, the increase in body-weight, the shrinkage in size of the spleen and of the liver, and the increase of the leucoblastic response. The relative proportion of serum globulin can be gauged by the aldehyde test, which is positive so long as the parasites remain active in the body and, moreover, persists for a period of two to three months after the patient has, to all external appearances, completely recovered. Lloyd and his collaborators have suggested that the serum-protein graph of kala-azar can be used as a serological test of the progress of the patient, just as the Wassermann reaction is employed in syphilis.

Even in cases reacting favourably to treatment, it is stated that apparently unchanged and viable parasites may be found in the spleen even after a gramme or more of antimony preparations have been injected. By the time the spleen has retracted within the costal margin, the Leishman-Donovan bodies have disappeared altogether.

1. Treatment with pentavalent compounds of antimony.—(*a*) *Stibacetin* (acetyl-*p*-aminophenyl stibiate of sodium) was originally prepared by the firm of von Heyden. This preparation was first used by Caronia in Sicily for the treatment of infantile kala-azar, and was afterwards used by the Editor in England. It has now been superseded by more complicated products.

(*b*) *Stibosan* (metachlor-para-acetylaminophenyl stibiate of sodium) (Bayer ; Meister-Lucius) was formerly known as von Heyden 471, and has been most extensively employed. The initial dose is 0·1 grm. (1½ gr.), but for robust individuals it may be as high as 0·2 grm. (3 gr.). The drug is obtainable in sealed ampoules containing 0·2–0·3 grm. each. The contents (a flocculent powder) are dissolved in a small quantity of freshly-distilled sterile water and can be given in a 5-per-cent. solution. Thus for 0·05 grm., 1 c.c. of fluid will be required ; for 0·1 grm. 2 c.c., and so on. For general use, however, it is safe to dissolve the drug in 10 c.c. of distilled water. The maximum individual dosage for an average person is 0·3 grm. (4½ gr.) ; in resistant cases 0·6 grm. (9 gr.) may be tolerated and is often successful where smaller doses fail. In weak patients the initial dose should be 0·05 grm. (¾ gr.), the maximum, 0·25 grm. (3¾ gr.). The injections may be given twice or three times weekly, and the number required to effect a cure will vary from 11 to 15. The requisite amount of stibosan is about 3 grm. for an adult weighing 100 lb., or about 5 grm. for an average European. Usually a case of average severity requires 7·5 grm., but, exceptionally, 15 or more grm. may be required. Children tolerate relatively large doses of the drug. At three years of age the maximum dose is 0·1 grm., the initial dose being 0·025 grm. increasing to 0·05, 0·075, and from twelve onwards 0·25 grm. In children between one and two years of age *intramuscular* injections up to 0·1 grm. can be given without causing more than

slight local pain. The presence of ascites is a contraindication to the use of the drug, but pulmonary complications, albuminuria and diarrhœa are not. Should jaundice occur, the injections should be discontinued. The advantage of stibosan is the diminished toxicity and rapidity of action as compared with tartar emetic. Severe reactions, fever, cough and vomiting are not usually encountered. The drug is stable and does not change in contact with air. For hospital use the drug is supplied in bottles of 10 grm.

(c) *Neostibosan* (formerly known as von Heyden 693) is the amino salt of para-aminophenylstibinic acid, contains 40 per cent. of metallic antimony, and is comparatively non-toxic, as is the preparation mentioned above. Batches of this drug are found to differ considerably, and the more recent preparations are known as Bayer 693B. It may be given in a strength of 25 per cent., either intravenously or intramuscularly. The doses may be given daily. The initial dose for an adult is 0·1 grm., the second 0·2 grm., the third 0·3 grm. This compound appears to be especially well tolerated. About ten injections are required for an average case, and a total of 2·7–4·0 grm. is usually necessary to effect a cure.

It has been pointed out by Neumann that in Malta, quite apart from the difficulties in administration, intravenous injections of antimony in children are apt to be followed by broncho-pneumonia, but neostibosan, when given intramuscularly, is almost equal to the intravenous method. A quantity of 2·5 grm. suffices within a period of six weeks. Since this method has been employed, noma has not been seen and broncho-pneumonia is less frequent.

(d) *Urea stibamine* (Stiburea—$C_7H_{12}O_6N_2Sb$), of which the dosage and spacing of the injections is usually the same as for *Stibosan*, is a compound of urea with stibamine (*p*-aminophenylstibinic acid), and was introduced by Brahmachari. This compound is apt to undergo chemical changes if exposed to the air. Urea stibamine is undoubtedly a very efficient preparation and often succeeds where other pentavalent salts fail; in resistant cases it may be given in the form of combined treatment. The Editor on several occasions has seen a successful issue from this method. The total amount requisite to effect a cure is about 3 grm. The usual length of treatment is one month; if, for some reason or other, an intermission in treatment takes place, the parasites tend to become antimony-fast. In 1925–1926, out of a total of 60,940 patients treated with this drug in Assam, 24,700 were discharged as cured. Urea stibamine may be given intramuscularly to infants in doses from 0·01–0·08 grm. in 1–2 c.c. distilled water, a total of 0·65 grm. being necessary.

(e) *Other antimony compounds* in use are *Antimosan* (von Heyden 661), *Stibamine-glucoside* (*Neostam*) and *Aminino-stiburea* (Union Drug Co. of Calcutta). The dosage and total number of injections are approximately the same as already outlined for stibosan, in fact it may be said that there is very little to choose between the various pentavalent compounds mentioned.

(*f*) *Solustibosan* 561 (pentavalent antimony hexonate) has been introduced by Kikuth and H. Schmidt, who consider it in many ways superior to neostibosan in the treatment of kala-azar. It is issued in ampoules of sterile soluble isotonic neutral solution in water so that 1 c.c. contains 20 mg. of antimony; thus 6 c.c. corresponds to a dose of 0·39 grm. of neostibosan and contains 0·126 grm. of antimony.

Kikuth has evolved a technique by which it is possible to use leishmania-infected hamsters for testing out this and other remedies. The animals are injected subcutaneously twice weekly for one or two weeks, the action of the

drug being controlled by liver puncture, and finally by examination of the organs post mortem, for the presence or absence of leishmania parasites.

Struthers and Yates have reported upon its application to man in China (Tsinan). They employed it on the basis that 2 c.c. of solustibosan is approximately equal to 0·1 grm. of neostibosan. The former has treated 29 and the latter nine cases. In some, it is said, the course was completed and a cure effected in nine days. This drug is usually given intravenously, though, being isotonic, it may also be injected by the intramuscular route.

(*g*) The preparation A.534 (Parke, Davis & Co.) is a pentavalent form of antimony combined with sulphur. The dose is 0·05–0·1 grm. Total dosage varies from 0·9 grm. to 1·45 grm. This method is now under trial.

Toxic effects of antimony treatment.—Christopherson states that "metallic taste in the mouth and throat need scarcely be considered as poisoning, but vomiting, giddiness, delirium, a considerable rise or fall in temperature, diarrhœa, and cramp in calves should be taken seriously. They are danger signals and, when they occur, the injections should be temporarily suspended. Rapid pulse, cold, clammy skin, signs of collapse, in fact, are serious symptoms of poisoning." Discomfort or pain in the chest, colic, headache, severe arthritic pains in shoulder and other joints, and even jaundice may be noted.

Disagreeable symptoms are less likely to ensue when the pentavalent compounds of antimony are used in preference to the trivalent. The death-rate among kala-azar patients has undoubtedly been much reduced (42 per cent. in 1925, according to Napier). Jaundice is, perhaps, more common in patients treated with the pentavalent compounds. It is by no means certain how antimony destroys the leishmania parasites; *in vitro* and also *in vivo* the action is certainly not a direct one.

2. Original method of treatment with trivalent compounds of antimony.—*Tartar emetic* (sodium-antimony tartrate). For the sake of completeness it is necessary to mention the original tartar-emetic treatment, as carried out on an extensive scale in India.

For routine use in India, tartar emetic is usually made up in a 2-per-cent. solution, the initial dose being ½ gr., increasing gradually to a maximum individual dose of 1¾ gr. (5·8 c.c. of the solution). As a general rule, Europeans can tolerate larger doses than the Indian; in the former the maximum individual dose is 2½ gr. An injection may be given every third day for two to three months. In children and in elderly patients the initial dose must be considerably smaller than that for those in more robust health, and should not exceed ½ c.c. (of the 2-per-cent. solution) per 10 lb. of body-weight. Therefore, for children under six years of age, 1 c.c. of the solution should be given for the first dose, and increased by ½ c.c. up to a maximum of 3 c.c. Three injections weekly can be given to a child of six months till a total of 4 gr. has been absorbed, and the injection may be made into the jugular vein, the head being allowed to hang over a table in order to make the vein prominent. In routine treatment of kala-azar in Assam, McCombie Young gave 30 gr. of tartar emetic over a period of three months. Bi-weekly injections are given with tabloids of the drug, which are dissolved in water so as to make 100 c.c. of a 1-per-cent. solution, of which 6 c.c. contain approxi-

mately 1 gr. According to Napier, the maximum dose of sodium- or potassium-antimony-tartrate to effect a cure, in any but a resistant case, is 60 gr. per 100 lb. of the patient's body-weight. In spite of the introduction of the pentavalent compounds, there are those who still believe in the efficacy of tartar emetic; for instance, Laurinich, in Naples, has treated 844 cases of kala-azar within twenty years in infants aged between one and one and a half years. The injections are given twice weekly and the average number varies between twenty and forty.

Intramuscular injection of antimony tartrate produces some local reaction culminating in necrosis and abscess-formation. The practice has therefore been abandoned.

Neoantimosan (*see* p. 725), or fouadin, has also been given by the intramuscular route, but the curative results are by no means satisfactory.

3. Subsidiary measures.—Various methods have been suggested with the object of increasing the leucocyte count and in this manner aiding drug treatment. Muir has advocated turpentine, and advised the injection of a mixture composed of turpentine 1 dr., creosote 1 dr., camphor 1 dr., olive oil 2½ dr. Of this, 0·5 c.c. are injected intramuscularly at frequent intervals. A more modern method which is being tried out is by injection of *pentanucleotide* as in true agranulocytosis, and Zia and Forkner have recorded recovery in four cases treated in this manner. Attention must be paid to the anæmia which is pronounced in longstanding infections. As a rule there is a definite reticulocyte response following upon antimony treatment, but in other cases a very definite anæmia persists, but yields to doses of iron, given either in the form of scale preparation (*Ferri et ammon. cit.*) or in massive doses of Blaud's pills. If flatulence and abdominal discomfort are not outstanding, a full and liberal meat diet should be given throughout the whole course of treatment, with the addition of fruit and vegetables.

Finally, as adjuvants to treatment, the expulsion of intestinal parasites, the treatment of coincident malaria by means of quinine, or atebrin, change to a healthy climate, good food, warmth, rest, physical comfort, and good hygienic conditions are indicated.

Resistant cases.—Resistant cases of kala-azar are occasionally encountered. In these cases the parasites are so numerous that the antimony treatment in the therapeutic doses fails to exert its customary effect. In such a contingency it is necessary to push the antimony injections to the limit of tolerance—that is to say, till toxic symptoms due to the drug are produced—in the case of the pentavalent compounds, in doses of 0·6 to 0·9 grm. Weekly intravenous injections of stabilarsan 0·3 grm., or neosalvarsan, appear also to be beneficial.

Prognosis.—Kala-azar is, in the great majority of cases, a chronic disease; but acute cases are noted in the early stages of an epidemic. Marked intestinal disturbance indicates a bad prognosis, as does also extreme leucopenia. The prognosis is naturally affected by coincident infections such as malaria, the dysenteries and ancylostomiasis. Napier has pointed out that with superadded pulmonary tuberculosis it is

especially grave; but there is a tendency for spontaneous cure to take place in about 10 per cent. of cases. The oft-repeated statement that owing to the introduction of the antimony treatment a 95-per-cent. mortality-rate has been converted to an equally high recovery-rate, is, therefore, not strictly true.

Prophylaxis.—Having regard to the character of the disease, in the endemic districts the cases should be dealt with as infectious: they should be isolated, and the houses and fomites should be disinfected or burnt. Domestic and personal cleanliness is of great importance. Infected dogs should be destroyed; in fact, in the endemic districts they should be kept away from association with man. By segregation of the sick, burning of houses, clothing, and furniture, etc., and provision of new huts, Price, Rogers, and Young have succeeded in exterminating the disease in infected coolie lines. Good results in prophylaxis have already followed the actual treatment of cases on a large scale. Should the sandfly prove to be the true vector, then energetic measures against that insect will have to be instigated (*see* p. 406).

II. ORIENTAL SORE

Synonyms. Tropical Sore; Bouton d'Orient; Delhi Boil; Cutaneous Leishmaniasis; Bouton de Biskra; Bouton de Bagdad; Aleppo Boil; Salek (Iran), etc.

Definition.—A specific ulcerating granuloma of the skin, endemic within certain limited areas in many warm countries. It is caused by a species of *Leishmania*, and is characterized by an initial papule which, after scaling and crusting over, generally breaks down into a slowly extending and very indolent ulcer. Healing after many months, it leaves a depressed scar. The sore is inoculable and, usually, protective against recurrence.

History.—In 1885 Cunningham first described certain deeply-staining parasitic bodies in mononuclear cells derived from these sores. Hoare has pointed out that it was Borovsky (1898), a military surgeon stationed at Tashkent, who first accurately described *Leishmania tropica*, and later (1902) Shulgin concluded that some night-biting insect was the intermediary host. J. H. Wright, in 1903, was ignorant of Borovsky's work, but he renamed the bodies *Helcosoma tropicum*. These observations have been abundantly confirmed, and the parasite is regarded as identical with the Leishman-Donovan body, and is known as *Leishmania tropica*. In 1907 Marzinowsky inoculated himself in Moscow with material obtained in the Caucasus, and reproduced a typical sore on his forearm.

Geographical and seasonal distribution.—Oriental sore occurs in Italy, where Vanni (1938) has recorded 300 cases in Abruzzi; Morocco; the Sahara (Biskra, Gafsa); Egypt (Zagazig, in the Nile Delta); Crete; Cyprus; Sicily; Asia Minor; Syria (Aleppo); Palestine (Jericho); the Sudan; Nigeria; Iraq (Bagdad); Arabia;

Iran; the Caucasus; India (Lahore, Multan, Delhi, Dera-Ismail-Kan, etc.); the Transcaspian Provinces; Turkestan (Tashkent and Bokhara); China, especially in Hunan. In South and Central America it is often, but not invariably, found in association with naso-pharyngeal leishmaniasis, especially in Peru, Bolivia, Brazil, the Guianas, and Mexico (Map III). In Australia it occurs in North Queensland.

In the tropics this form of ulceration is especially prevalent about the commencement of the cool season; in more temperate climates, towards the end of summer or beginning of autumn. Years of prevalence may be succeeded by years of comparative rarity—possibly in harmony with altered sanitary conditions. In Delhi, for example, in 1864, from 40 to 70 per cent. of the resident Europeans were affected with the local sore; on certain sanitary improvements being effected, the frequency of the disease was immediately materially reduced.

Epidemiology and endemiology.—Although oriental sore may occur in countries where kala-azar is endemic, its distribution is as a rule quite distinct (*see* Map III). It has been pointed out that in India cutaneous leishmaniasis is confined to the west, whereas kala-azar is endemic on the east coast. In North Africa oriental sore occurs north of latitude 35°, whereas kala-azar is found south of this line. In Iran and Iraq, where oriental sore is very common, cases of kala-azar are absent. Central Asia is an exception, for according to Gerschenowitsch, they are found side by side, even in a single family, and both diseases have been seen in the same patient. Apparently also recovery from cutaneous infection does not necessarily protect against subsequent infection by the kala-azar parasite.

In the endemic areas, oriental sore appears to have a seasonal preference, making its appearance between September and January; in cities like Aleppo and Bagdad, where the disease is very common, children usually acquire it between 2 and 3 years of age, and it appears to be quite exceptional for any native to attain maturity without having had one or more of these sores. In fact, it may be said that every woman in Bagdad bears on her face marks of the ravages of this disease.

Oriental sore occurs as a natural disease in dogs and cats. The organism has been demonstrated in cutaneous sores on the ears, lips, nose and inner canthus of the eye of these animals in Teheran, Tashkent, Iraq (where it is only seen during the winter months) (Machattie, Mills and Chadwick), and recently in South America and India; while Sinton has shown that the leishmania sores occurring in the noses of dogs in India are transmissible to man. *Macaca* monkeys are easily inoculated and may act as reservoirs of infection. Oriental sore has been found as a natural infection of the brown bear in Turkestan, and also on the nose of a horse by Bennett in Kordofan, Sudan. An allied form (*L. myoxi*) occurs in the dormouse.

Ætiology.—Section of the papule displays an infiltration of the derma by a mass of small round granulation cells. These lie between

the normal elements of the tissue, particularly about blood-vessels, lymphatics, and sweat-glands; towards the centre of the lesion they completely replace the normal structures. The parasites are found in the granulation tissue at the edge of the lesion, and may be demonstrated in scrapings; care must be taken to avoid obtaining too much blood. The parasites (*Leishmania tropica*) sometimes occur in rosettes or aggregated masses of as many as a hundred individuals and are often enclosed in macrophage cells or in leucocytes; giant cells are frequently found in the deeper layers.

The cultivation of the parasite, first carried out by Nicolle, is easily effected in the N.N.N. medium in the same manner as is kala-azar. The surface of a non-ulcerating sore is first painted with iodine and then punctured with a fine glass pipette, in order to collect material for inoculation. The parasites, as in the case of *L. donovani*, grow best in the condensation water. In heavy infections, flagellates appear in forty-eight hours, but in scanty ones not for three weeks or more.

The parasites undergo the same changes in culture as do *L. donovani*, but it has been remarked that they are able to flourish in conjunction with contaminating micrococci, which the parasites of kala-azar are unable to do. Noguchi has shown that the addition of immune serum from an experimentally-inoculated rabbit causes the organism to grow in clumps.

Transmission.—Epidemiological considerations suggest that the infection is disseminated by the agency of some small biting fly. Wenyon, in 1911, first suggested the sandfly (*Phlebotomus*) as the possible vector in Bagdad, and he found that 6 per cent. of these insects caught in Aleppo had a flagellate of the *Leptomonas* type in their intestinal canals—an observation which has been confirmed in India and elsewhere. More definite evidence was brought forward by the Sergents, Parrot, Donatien and Béguet (1921), who have described the production of an oriental sore on the arm of a man in Algiers two and a half months after the scarified skin had been treated with a saline suspension of crushed *Phlebotomus papatasii* which had been collected three or four days previously. The convincing part of this experiment is that the sandflies were caught in Biskra, an oasis where oriental sore is very common, and transported 600 kilometres to Algiers, where the disease does not occur. Of the great number originally caught, only seven remained alive, and these were used for the experiment.

These experiments have been successfully repeated by Adler and Theodor in Palestine with an *Herpetomonas* found as a natural infection in the same species of sandfly. In Palestine, according to the former, *L. tropica* has adapted itself to *P. papatasii*, and the infection is acquired usually from crushing the sandfly, and thus inoculating the parasites into the skin. In Bagdad and in India the parasite is more completely adapted to *P. sergenti* and is transmitted by the bite of that insect. Berberian has shown that *Stomoxys calcitrans*, which is attracted to sores and readily feeds on them, is capable of transmitting oriental sore mechanically.

Monkeys and dogs have proved to be experimentally inoculable while donkeys, horses, goats, and sheep are refractory.

As a rule, second attacks do not occur. Observing this, the Jews of Bagdad at one time practised on their young children oriental-sore inoculation.

Neither race, nor sex, nor age, nor occupation, nor social condition materially influences susceptibility.

Relationship of kala-azar to oriental sore.—Manson suggested that the relationship between oriental sore and kala-azar might be compared to that of vaccinia and variola. He based his view upon the immunity produced by one attack of oriental sore against further infections of the same disease; and upon the well-recognized dissimilarity in the distribution of these two diseases, for in India, where kala-azar is common, oriental sore is rare, and *vice versa*. If the parasite of kala-azar is identical with that of oriental sore (*Leishmania tropica*), then the parasite must in some way have been deprived of its virulence; for whereas kala-azar is often a fatal disease, oriental sore is eminently benign. In view of these facts, Manson suggested that inoculation with cultures of *L. tropica* might confer a protection against subsequent infection with kala-azar, and that this method might be used as a prophylactic.

The suggestion has to a certain degree proved true, for Nicolle has succeeded in producing some amount of immunity to generalized leishmaniasis in dogs and monkeys by injecting them intraperitoneally with cultures of *L. tropica*.

Kirk has, however, reported the occurrence of oriental sore and kala-azar in the same subject from the Blue Nile district of the Sudan. (*See also* p. 198.)

Incubation period and constitutional symptoms.—The incubation period of oriental sore is variously stated in days, weeks, or months. That it may be a brief one, a few days or weeks, seems to be established by the appearance of the sore within a short time of arrival in endemic districts, or after inoculation. That it can be of much longer duration is equally certain. Manson saw an unquestionable oriental sore which did not appear until five months after the patient had been exposed to any possibility of infection. Wenyon inoculated himself with oriental sore in Aleppo; it was not until six and a half months later that a leishmania-containing papule, subsequently developing into a sore, appeared at the site of inoculation. In other cases the incubation period appears to be as much as fifteen months, or even longer. Sometimes eruption of the sores is accompanied by fever and other constitutional symptoms, and temperatures up to 103° F. have occasionally been noted.

Symptoms.—The local lesion in oriental sore commences as a minute itching papule which tends to expand somewhat as a shotty, congested infiltration of the derma. After a few days or weeks the surface of the papule becomes covered with fine, papery scales. At first these scales are dry and white; later they are moister, thicker, browner, and adherent. In this way, a crust is formed which, on falling off, or on being scratched off, uncovers a shallow ulcer (Fig. 27).

The sore now slowly extends, discharging a scanty ichorous material; this from time to time may become inspissated, and a crust forms, while the sore continues to spread underneath. The ulcer extends by the erosion of its perpendicular, sharp-cut, and jagged edge, which is surrounded by an areola of congestion. Subsidiary sores may arise around the parent ulcer, into which they ultimately merge.

Fig. 27.—Oriental sore. (*After Wenyon. Photo: R. McKay, reproduced in "Journ. Lond. School Trop. Med."*)

These sores, usually about an inch in diameter, may come, in some instances, to occupy an area several inches across.

After a variable period, ranging from two or three to twelve or even more months, healing sets in. Granulation is slow and frequently interrupted. Often it commences at the centre while the ulcer may be still extending at the edge; often it is effected under a crust. Ultimately a depressed white or pinkish cicatrix is formed. Contraction of the scar may cause considerable and unsightly deformity.

Oriental sore may be single or multiple (Fig. 28). Two or three sores are not uncommon; in rare instances as many as one hundred and fifty have been counted on the same patient. They are mostly situated on uncovered parts—hands, feet, arms, legs, and, especially in young children, on the face; rarely on the trunk; never on the palms, soles, or hairy scalp. Occasionally these ulcers may occur on the ears, tip of the nose, and lower lip. A small multiple diffuse form may resemble diffuse papillomata. Very rarely these sores occur on the buttocks or on the perineum. Recently the Editor investigated a case with Mr. P. Lockhart-Mummery in which a diffuse indurated

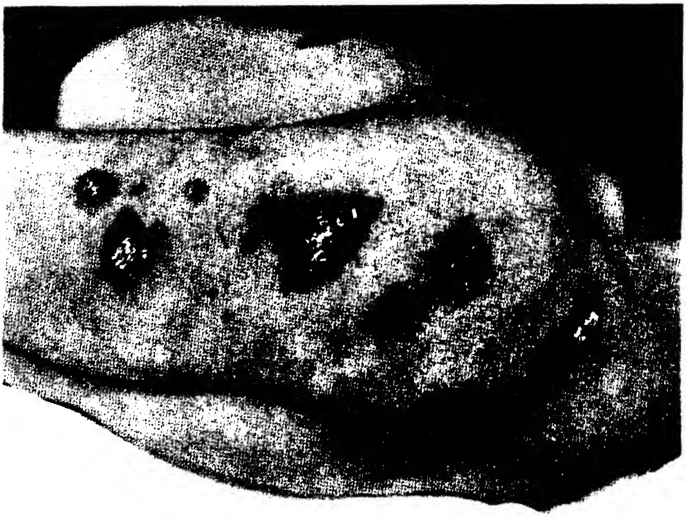


Fig. 28.—Diffuse cutaneous leishmanial lesions on arm. (*After Byron Evans.*)

swelling in the immediate vicinity of the anus was found to be of this nature.

In a very few instances the initial papule does not proceed to ulceration, but persists as a scaling or scabbing, non-ulcerating, flattened plaque—just as sometimes happens in the case of the primary sore of syphilis. Sometimes the ulcer is quite superficial, an erosion rather than an ulcer. Occasionally, from contamination with the virus of some other infectious acute inflammatory skin disease, the primary lesion may become complicated, and perhaps a source of serious danger. Otherwise, oriental sore is troublesome and unsightly rather than painful or dangerous. When ulcerated, or secondarily infected, the lymphatic glands in the immediate vicinity may be enlarged, and the Editor has observed multiple cystic swellings of the lymphatic vessels in the area of the sore which on incision exuded sterile pus.

Associated subcutaneous nodules have frequently been described. Thus Byron Evans (1938) in a case of extensive cutaneous leishmaniasis found, around the arm lesions, five separate apple-jelly-like papules. Others were associated around similar lesions on the opposite arm or leg; in size they varied from 0·25–1 cm. in diameter; they were firm, discrete and freely movable and were not tender. On removal, they showed chronic inflammation with fibrosis, and the presence of Leishman-Donovan bodies, suggesting a chronic lymphatic infection with Leishmania and denoting the spread of the infection via the lymphatic route. These nodules were described as early as 1847 by Poggioli and by Bonne (1901), also, in association with South American leishmaniasis by Darier, de Christmas, Escomel and Werner.

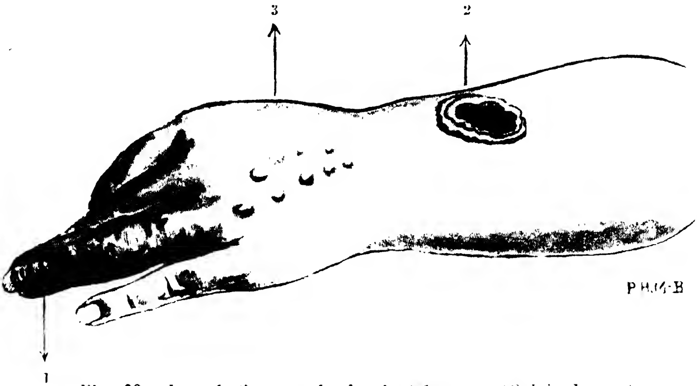


Fig. 29. Lymphatic spread of oriental sore. (*Original case.*)
1, Primary sore on finger; 2, secondary crateriform sore on wrist; 3, nodules in course of lymphatics.

In Christopherson's case (1923) twenty-five vesicular lumps of varying sizes were noted which contained leishmania, while the Editor found similar swellings on the dorsum of the hand and over the submental gland in his case (Fig. 29). Gonzalez, Boggino and Rivarola have also described a similar case in 1937. It is to be noted that a sharp bout of pyrexia (T. 103–104° F.) frequently precedes the appearance of these nodules.

Differential diagnosis has to be made from tuberculides of the hypoderm, including Bazin's disease.

Verrucose form.—A peculiar kind of dermal leishmaniasis has, under the name of parasitic granuloma, been described by Ferguson and Richards as occurring in Egypt (Fig. 30). These lesions, which usually affect the lower extremities, resemble warty out-growths or papules; they may be solitary or multiple, and may be the result of auto-inoculation. They are best treated by excision.

Lupus-like lesions.—Christopherson has described discrete lupus-

like nodules occurring on the cheek, in general appearance resembling lupus vulgaris, but containing Leishman-Donovan bodies. A cheloid form has also been described. On the other hand, the Editor has observed typical apple-jelly lupus nodules arising in the scar tissue of a healing leishmanial sore. Similar cases have also been recorded at the London Hospital.

Generalized non-ulcerating form (dermal leishmanoid).—Brahmachari has described papillomatous nodules occurring over the whole of the body, due to Leishman-Donovan bodies, which at first were thought to be tubercular leprosy. Four cases had been observed in India,

Fig. 30. Diffuse cutaneous leishmaniasis of the leg in an Egyptian.
(Ferguson and Richards. By permission of Liverpool School of Trop. Med.)

all of whom had been treated previously for kala-azar and had apparently recovered after antimony injections. It was originally suggested that these skin lesions are caused by *L. donovani* which has been modified by antimony treatment, but this view is by no means established as correct. Provisionally, this form is here described as separate from kala-azar. Christophers, in 1904, gave an account of similar papular lesions occurring on the thighs and scrotum, arms and neck, in undoubted cases of kala-azar (*see* p. 186).

Diagnosis.—On clinical grounds these sores have to be distinguished from the desert or veld sore (p. 679), tertiary syphilis, ulcus tropicum, lupus vulgaris, and blastomycosis. The distribution

of the sores and the presence of the Leishman-Donovan body render the diagnosis a matter of no very great difficulty. The parasites are best demonstrated by sterilizing the skin at the edge of the ulcer, and running in a fine glass pipette through a puncture made in the skin, with the object of getting beneath the ulcer, so as to obtain serum and tissue cells—but not blood—if possible, free from bacterial contamination. This is a much better method than scraping the surface of the ulcer with a blunt needle or with a fine knife. The cultural method may also be employed. Care must be taken to distinguish the Leishman-Donovan bodies from yeasts which are sometimes present in cutaneous ulcers and may simulate them.

Napier's aldehyde test, in contradistinction to kala-azar, is negative.

Treatment

The treatment of oriental sores in general, especially in a temperate climate, does not, as a rule, entail any particular difficulties, for the reaction of the tissues to the particularly indolent ulceration depends to some extent upon the general nutrition and environmental conditions. When once removed from the endemic area, the disease tends to disappear spontaneously in about one year.

(*a*) **General measures.**—When the sores are multiple, as they so often are, and when they are situated on the extremities, undoubtedly the best treatment is intravenous injections of antimony, especially the pentavalent compounds as already outlined (p. 193). Antimony tartrate is efficacious (sodium antimony tartrate) in 2-per-cent. solution, and the total amount necessary is, as a rule, 15 gr. (1 grm.). Of the pentavalent preparations, *Neostibosan* or *Neostam* are equally suitable and, when feasible, should be given intravenously in doses commencing with 0·1 grm. and increasing on alternate days to 0·3 and 0·4 grm. Much smaller total quantities are necessary to effect a cure than in kala-azar. Generally a total of 1–2 grm. suffices. Vigne and other French authors recommend intravenous iodobismuthate of quinine (3 c.c.) twice weekly. For women and children, in whom injections cannot be given intravenously, the intramuscular route should be chosen, as mentioned on p. 194. Raymond and Cruickshank, in an account of an epidemic of these sores following the Quetta earthquake, found injection of trivalent antimony compounds (tartar emetic and fouadin) combined with local *scraping* the most effective method. The pentavalent antimony preparations were less satisfactory under these conditions.

(*b*) **Local measures.**—When the sores are situated on the face—eyebrows, nose, cheeks, lips—and other situations, especially on the hands, when on account of their chronicity, induration and secondary infection, the antimony is unable to act upon the parasites, then intravenous injections of this remedy are by no means so effective.

Secondary infection is a most important element and in these

infected cases no treatment is of any avail until the scabs have been removed and the septic element removed by hot fomentations, eusol dressings, and the application of nitrate-of-mercury ointment. This aspect of the treatment of oriental sores is one that is not sufficiently realized or appreciated. The chief difficulty in describing the treatment of this condition is the number of remedies which have been advocated and which from time to time have been found to be efficacious.

Ointments.—Various applications have been found useful on different occasions, e.g. *Cignolin* (a refined product of chrysophanic acid, *see* p. 690), in the following formula:

℞	Cignolin	gr. iv	(0·259 grm.)
	Ichthyol	gr. viii	(0·518 grm.)
	Ol. cadini	♏ xl	(2·368 c.c.)
	Benzoli rect. ad	℥i	(28·42 c.c.)

Ft. pigmentum: To be applied to sore every day.

This solution in the form of a paint should be applied to the sore with a camel-hair brush, care being taken not to overlap on to the surrounding skin. This should be repeated daily for 2–4 weeks, after the sores have been cleaned up with eusol dressings or boric fomentations. This form of treatment is especially applicable to children when the sores are situated on the face, and the Editor has had the most striking and favourable results from this simple method.

Another method is to apply the Cignolin and to cover it with granular paraffin wax, which is applied until it solidifies.

Other ointments which have been recommended are: *Pellidol* (Bayer), containing 2-per-cent. diacetylamine-azol-toluol, *Desitin* (Klinke) (chlorine and cod-liver-oil salve), and *Orisol* ointment, which contains berberine sulphate. Good results have been reported by the local application of phosphorated oil and also by finely-powdered permanganate of potash. Kassirsky, in Tashkent, has found an ointment prepared from the whole seeds of *Ricinus* (of which the active principle is ricin), ground up and mixed with 10-per-cent. vaseline ointment, effective. It is applied every few days to the ulcer. The first applications cause considerable irritation.

Injections into the base of the sores.—These methods of treatment probably act by causing a tissue reaction, but as a rule injections are painful and, on account of the surrounding inflammation, cannot be used for sores on the face, especially in the vicinity of the eyes.

Treatment by injection of emetine.—Photinos reported good results from local injections of emetine hydrochloride, and Sinderson in Iraq used a 2-per-cent. solution which should be injected so as to reach every part of the sore, so that in large ulcerations it may be necessary to puncture in three or four places. The needle of the syringe is inserted into the healthy skin and passed through the tissues. The solution is injected, the needle being gradually withdrawn at the same time. Following the injection the puncture site is sealed with cotton-wool and collodion flexile. When ulceration is deep, healing may not be complete for a month. A local inflammation is

thereby set up, with the disappearance of the parasites from the lesion. The lesions usually clear up in fifteen to thirty days.

Injections of berberine sulphate.—Subcutaneous injections of berberine sulphate (*Karamchandani*) have been used extensively in India. A quarter of a grain is dissolved in 1·5 c.c. distilled water and injected in the immediate vicinity of the sore. Two to four injections, when combined with dressings of hypertonic saline, usually suffice. The amount of berberine sulphate is not injected in one spot, but at four or more points round the sore. The solutions are very stable and can be preserved in sterile tubes with rubber caps. Hamilton Browne and Deri state that if the sore is not healed within a week, treatment must be repeated, but a third course is rarely necessary. Berberine acid sulphate is put up by Messrs. May & Baker in a 2-per-cent. solution under the name of "Orisol" and it is claimed by Gupta that 2–3 c.c., injected into several points, will cure the majority of sores. This method has the disadvantage of being somewhat painful.

Treatment of indolent sores on the nose.—These require special mention as, on account of the induration of the surrounding tissues, they appear to be especially refractory and in this situation they do not appear to respond to the applications which are efficacious in other situations. After being cleansed, the base of these sores should be scraped by a Volkmann's spoon and dilute nitrate-of-mercury ointment thoroughly rubbed in. Dry dressings or powdered permanganate of potash should subsequently be applied.

Treatment by vaccines made from dead cultures of *Leishmania* has been successfully practised by Schwartzmann, Chodukin, and others. The vaccine consists of a saline suspension of washed flagellates killed by heat.

Treatment by X-rays.—When available, this line of treatment appears to be at once rapid and efficacious. In Iraq it is stated that a single full-pastille dose of X-rays produces a cure within ten days in the majority of cases. The rays act directly upon the Leishman-Donovan body, penetrating the unbroken skin, and thus being efficient in non-ulcerated as well as in ulcerated sores. This treatment is not followed by any constitutional disturbance, and the scars which are left are hardly noticeable. The apparatus necessary is a coil giving a 16-in. spark with a mercury jet interrupter. Macalaster-Wiggin tubes with 7-in. bulbs are found to be most satisfactory. The rays are directed on to the affected area through a lead glass cylinder an aluminium filter 3 mm. in thickness being interposed, and the surrounding healthy skin protected by properly shaped pieces of leaded rubber. The Sabouraud unit is used and is estimated by exposing barium platino-cyanide pastilles. The current of the secondary circuit should be 1·25 ma., with a vacuum corresponding to a hardness of 8·9 on the Wehnelt scale. With the apparatus described, a Sabouraud unit requires an exposure of twelve minutes, which is found in most cases to effect a cure.

Treatment by ionization.—This has been found to give satisfactory results. The ulcer is cleaned and covered with a pad consisting

of sixteen layers of lint soaked in 2-per-cent. zinc-sulphate solution; this is firmly applied under a zinc electrode by means of a bandage. and then connected with the positive pole of an electric current which is supplied by eighteen accumulators giving an average of 36–38 volts. A patient with a sore of an area of 1 in. in diameter can easily stand 10 ma. as gauged by a resistance coil. The application is continued for twenty minutes, the pad being constantly moistened with zinc-sulphate solution.

Treatment with carbon-dioxide snow.—In Lahore, Central India, the application of carbon-dioxide snow constitutes the sole form of treatment. This should be applied for 5–30 secs., depending upon the size of the lesions; the application is repeated every ten days.

Prophylaxis.—In the endemic areas of the disease, measures should be taken in the form of insect repellents (*see* p. 134) to protect the exposed parts against bites of phlebotomus. At night-time a fine-mesh netting, forty-five holes to the square inch, is necessary to exclude these insects (*see* Fig. 12). Dogs with suspicious-looking sores should not be permitted in the vicinity of human dwellings. In the East it is still generally believed that infection may be conveyed by laundry which has been washed by natives who are infected with these sores. Prophylactic inoculation with cultures of *Leishmania tropica* has been practised in south-east Russia (Lawrow and Dubowskoj). Sores develop at the site of inoculation after an incubation period of two to six months. The immunity thus produced protects against further infection.

III. LEISHMANIASIS AMERICANA

Synonyms.—Espundia; Bubas Braziliana; Uta; Pian Bois; Forest Yaws (British Guiana); Bosch Yaws; Naso-pharyngeal Leishmaniasis.

History.—Under the names specified, several writers describe a very grave form of leishmaniasis occurring in certain South American countries; isolated cases resembling the American disease have been reported from the Sudan (Christopherson), Somaliland and Italy, but possibly in these it merely represents a secondary invasion of the mucous membranes from the surrounding skin. Mutilations of the face reminiscent of this disease have been found in figures engraved on old Inca pottery.

Geographical distribution.—The most northerly point from which this form of leishmaniasis has been reported is the Peninsula of Yucatan, about 21° north latitude, and the most southerly 30° south in the Argentine. It is prevalent in the northern part of Argentina and in Paraguay at 25° south. Probably the centres of its greatest prevalence are in the states of São Paulo and Bahia in Brazil, and in parts of Peru between 5° and 25° south. Altitude is a limiting factor. Most of the territory has an elevation of less than 2,000 feet. Heat and moisture are necessary for its existence. In the chicle forests of Yucatan the infection is contracted in the rainy season.

In Rio de Janeiro, however, the disease is common in the residential

section. It has been reported from the West Indies (Martinique), Mexico (State of Campeche), and Yucatan, British Honduras, Honduras, Guatemala, Colombia, British, Dutch and French Guiana, Brazil, Uruguay, Argentina, Paraguay, Peru, Bolivia and Ecuador (Map III).

In Paraguay the disease has assumed epidemic characters, and a large proportion of the population in certain districts, and 70–80 per cent. of prospecting parties, have become affected, so that most drastic public measures have had to be taken to prevent its spread. It is usually seen in men working in the forests, especially gum-pickers. A similar disease has been observed in the dog in the endemic centres, and it is possible that it occurs in the agouti (*Dasyprocta*).

Ætiology and symptoms.—The disease occurs at any age in either sex, in strangers as well as in the indigenous population: it begins as a sore on some mucous surface. The sore is of the chancrous form of the ordinary oriental-sore type. It heals in time, leaving a characteristic scar. After an interval of months or years, fungating and eroding ulcers (Fig. 31) of a most intractable character break out on the tongue, and in the buccal and nasal cavities, destroying and obstructing them, and ultimately, if untreated by antimony, leading to the death of the patient by exhaustion after years of suffering. The lymphatic glands are often involved, but the abdominal and thoracic organs are spared. Though affecting the mucous membranes in this characteristic manner in the endemic zones, the ulcers, as in oriental sore, occur in other uncovered parts of the body. They have been commonly noted on the pinna of the ear in gum-pickers (*oreja de chichleros*). For the state of São Paulo, Brumpt and Pedroso record localization of sores as follows (in percentages): Leg 30, foot 12, forearm 12, head 11, hand 10, hip 4, elbow 4, trunk 3, nasal mucosa 3, knee 2, buccal mucosa 2, neck 2, arm 1, pubes 1.

Fig. 31. — Leishmaniasis Americana affecting the nose and upper lip. (*Bernasconi and Paterson.*)

Leishman bodies are to be found, though not in great profusion, in scrapings and sections of the fungating ulcers, and present no morphological differences from *L. tropica* or *L. donovani*, but have been distinguished by Vianna as *Leishmania braziliensis*. Giant cells and flagellated forms of the parasite have been found in sections. It is

believed that the original sore in this grave form of leishmaniasis develops at the site of the bite of a jungle insect, probably a sandfly—*Phlebotomus*—and the following species are suspected (Shattuck, 1935) : *P. squamipes* (Dutch Guiana and Brazil) ; *P. intermedius* (Brazil and Argentina) ; *P. migonei* (Venezuela, Brazil, Paraguay and Argentina).

Diagnosis is made upon the typical clinical appearances and the discovery of the parasite. Espundia has to be distinguished from the ulceration of yaws (gangosa) and syphilis. In ulcerated lesions the crust should be removed and smears made from the underlying sero-purulent discharge.

The excision of a piece of granulation tissue and the expression of the contained serum on a slide often afford a more ready method of diagnosis. In five cases discovered in the Sudan Humphreys and Mayne found the leishmania in material obtained by pinching the lobulated growths, but not by splenic puncture, as there was coincidental enlargement of this organ.

These sores infiltrate deeply into the tissues, and besides grave destruction of the nose, lips, and tongue, they may be followed by secondary infections, such as erysipelas and even gangrene.

Treatment.—The general treatment is that of oriental sore, and was introduced by Vianna in 1912; ten to twenty intravenous injections of antimony tartrate (20–30 gr.) generally suffice for a cure. The local ulcers on the lips and nose are cleaned up with fomentations, the cleansed surfaces anæsthetized with a mixture of cocaine, menthol, and carbolic acid, then sprinkled with finely powdered antimony tartrate and bound up with a bandage. Subsequently the wounds are dressed with an ointment composed of zinc oxide, bismuth, and lanolin. In the case of the buccal mucosa, scabs must be removed with a solution of bicarbonate of soda, the surface anæsthetized with cocaine (1-per-cent.) and sprayed with 1–2-per-cent. antimony-tartrate solution. Every four to eight days the tartrate is used in a saturated solution, the application being made by means of a pledget of cotton-wool.

Mazza and others in northern Argentina have succeeded in obtaining good results in the treatment of muco-cutaneous leishmaniasis with intramuscular injections of *Fouadin* (Bayer), a trivalent antimony compound, in doses varying from 0·5 to 5 c.c. The treatment was continued for varying periods. Twenty to thirty injections are usually necessary and, according to Schulemann, the results continue to be highly satisfactory.

Good results have recently been obtained by intramuscular injections of *Eparseno* (dioxy-diamido-arsenobenzol), prepared by Poulenc Frères, Paris. Injections of 0·12 to 0·25 grm. (1–2 c.c.) are given and as many as 10–20 injections at intervals of two to three days are necessary to effect a cure. Others have obtained success with similar injections of the double iodide of quinine and bismuth (0·15 grm. daily for one month).

Subsection B.—FEVERS CAUSED BY BLOOD SPIROCHÆTES AND SPIRILLA

CHAPTER VI

RELAPSING FEVERS

Synonyms.—Febris Recurrens; Spirillum Fever; Famine Fever; Tick Fever; Bilious Typhoid of Griesinger.

Definition.—An acute infectious disease, or, possibly, a group of infectious diseases, characterized by fever of sudden onset and, after several days (one to seven), rapid subsidence, which may relapse at intervals of from one to seven or more days for an indefinite number of times. It is caused by spirochætes which are present in the blood during the fever and are transmitted by certain insects (body-louse) or by certain ticks (*Ornithodorus*).

History.—Relapsing fever was known to Hippocrates. In 1873 Obermeier discovered the spirochæte now known as *recurrentis*, vel *obermeieri*. In 1904 Philip Ross and Milne in Uganda, and rather later, but independently, Dutton and Todd on the Congo, discovered that in Africa the spirochæte was communicated by the bite of a tick, *Ornithodorus moubata*. The last two observers found that the parasite could pass into the egg and larva, and so confer infective powers on the mature tick of the succeeding generation. In 1907 Mackie recorded an outbreak of relapsing fever in which lice, *Pediculus humanus* var. *corporis* and *capitis*, apparently served as the transmitting agents—a view favoured by the experiments of Nicolle and others. In 1921 Bates, Dunn, and St. John proved that under experimental conditions the ticks *Ornithodorus talaje* and *O. venezuelensis* convey the disease in Panama and in Venezuela. A Spanish form described by de Buen occurs in Southern Spain and Morocco and is transmitted by *O. marocanus*, which lives mostly in the burrows of rats and porcupines and the earths of foxes, and also frequents pigsties. Since then Herms has described a distinctive tick-borne form in California, and Adler a similar ornithodorus-conveyed disease in Palestine.

Geographical distribution.—In Europe relapsing fever occurs from time to time in the British Isles, but especially in Ireland, and in Norway, Denmark, Germany, Russia, and Turkey. In Africa the disease has long been known in Egypt, while Dutton and others found a specially virulent form widely spread in Central Africa (tick fever) in the Congo, East Africa, Uganda, Abyssinia, and Madagascar. In Asia it is met with in Iran, and in India, where in 1922 large

epidemics occurred in the Central Provinces and North-Western Frontier, and it is of frequent occurrence in China. Epidemics have been recorded in the United States, especially in Texas, and recently in Senegal and French Equatorial Africa, China and Manchuria, while a special tick-borne form of the disease is now recognized in California as well as in the northern states of Central and South America, Spain, Morocco and Palestine.

Ætiology.—It has been definitely proved that the various forms of relapsing fever are caused by *Spirochæta recurrentis*, and organisms which are morphologically indistinguishable from it but which may be biologically distinguishable, such as *S. duttoni* and *S. venezuelensis*.

Typically, the spirochæta is a delicate spiral filament; its length varies from 8 to 15 μ, and its width from 0·2 μ to 0·3 μ. Each turn has an amplitude of 2 to 3 μ. The body of the parasite may have three, four, or six bends or turns; dividing forms appear to have more; in fact, the body of the spirochæte undulates, it does not strictly form a spiral. Coles describes the minute structure as consisting of small granules in a containing tube. By the Romanowsky method the body of the parasite usually stains uniformly, with the exception of the extremities, which are pointed and take only a very faint tint. In fresh blood the spirochætes exhibit very active screw-like movement; some are longer than others, the long forms resulting from end-to-end attachment of two or more parasites. That this is the explanation of the long forms, which may measure from 16 to 100 μ, is shown by staining. In those measuring from 16 to 18 μ we find a pointed extremity at each end of the filament and a pale zone in the middle, the pale zone corresponding to the approximated lightly staining extremities. The still longer forms admit of a similar explanation. Although the normal habitat of the spirochætes is the liquor sanguinis, occasionally in fresh liquid blood preparations they are seen within the red blood-corpuscles, though this probably does not occur within the body.

Great variation is shown in the morphology of the spirochætes, but there is a consensus of opinion now that no constant morphological distinctions exist between the organisms occurring in the different clinical forms of the disease. For an explanation of the nomenclature the reader is referred to p. 891.

Demonstration of the parasite.—It is necessary to remember that the parasite occurs in the blood during the febrile stage of the disease only, often disappearing forty-eight hours before the crisis and being very scarce or absent entirely during the non-febrile intervals. In some forms and cases of the disease it is present in large numbers in every field of the microscope: in other forms and cases it is so scanty that many fields have to be examined before a single specimen can be discovered. In thin films of fresh blood its presence can usually be recognized from the agitation its movements communicate to the adjacent corpuscles (Fig. 32.) In dried and fixed films the stains in general use for malaria work suffice.

It has been pointed out that it is especially in children that the spirochætes may be found, in the blood-stream during the apyretic periods.

The dark-ground method of illumination is admirably adapted for demonstrating these parasites in a living state; a very strong illuminant, preferably a high-power electric-light—not always procurable in the tropics—is required. Occasionally, when very scarce in the blood-stream, as during a relapse, or in the clinical form of the disease met with in North Africa, the organism may best be demonstrated by the "thick-film" method.

Cultivation.—The successful cultivation of *S. recurrentis* and its sub-varieties has been effected by Noguchi and others in sterile ascitic fluid containing citrated blood and a small amount of fresh kidney, incubated at 37° C. The greatest multiplication of the organisms takes place at the junction of the ascitic fluid and of the blood. Anäerobiosis is necessary and also the presence of coagulated albumin. The *p*H value is of great importance. The spirochætes reach their maximum development on the seventh to the ninth day, after which they begin to disintegrate. Subcultures retain their virulence for mice.

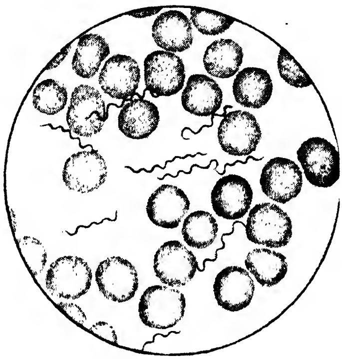


Fig. 32.—*Spirochæta recurrentis* **in blood-film.** × 500. (*Photomicro: Dr. John Bell.*)

Different strains of relapsing-fever parasites.—It is undoubtedly the case that in one part of the world the spirochæte of man is transmitted by one species of blood-sucking arthropod, and in another part of the world by another; that the serum reactions of these parasites differ; and that the fevers they cause are, in some respects, different clinically. The parasite, as originally described in Europe, is known as *S. recurrentis*. Attempts have been made to separate the North American form under the name of *S. novyi*, the Indian form as *S. carteri*, and the North African form as *S. berbera*, though these distinctions do not appear to be valid. The parasite of the Iranian form of the disease (mianeh fever), which is thought to be clinically distinct, is known as *S. persica*, and that of the Central African disease, popularly known as tick fever (or carapata disease) as *S. duttoni*. The South American form is known as *S. venezuelensis*, that of Panama as *S. neotropicalis*. In 1926 de Buen described a new variety, more resembling the Central African form, which is transmitted by a tick (*Ornithodorus marocanus*) which lives in the burrows of rats and porcupines, and the parasite has been named *S. hispanica*; but according to Delanöe, the Moroccan spirochæte differs slightly, and he has proposed the name *S. marocana*. In Turkestan a Russian strain is said to be transmitted by *O. papillipes*, which has also been proved to be the carrier in Palestine. Clark and Graham suggested that a tick-borne infection might occur in the Colorado Valley, Texas.

SYNOPTICAL TABLE OF VARIOUS STRAINS OF *SPIROCHÆTA* AND CLINICAL SYMPTOMS OF THE RELAPSING FEVERS THEY EVOKE IN MAN

Habitat and strain.	COSMOPOLITAN: N. AND S. AMERICA. N. AND W. AFRICA. N. CHINA. EUROPE. INDIA. *Spirochæta recurrentis (obermeieri, novyi).*	IRAN AND NORTH-WEST INDIA. *Spirochæta persica.*	PALESTINE. *Spirochæta sogdianum.*	SOUTH SPAIN AND MOROCCO. *Spirochæta hispanica.*	CENTRAL AFRICA. *Spirochæta duttoni.*	CALIFORNIA. *Spirochæta turicatæ.*	CENTRAL (PANAMA) AND S. AMERICA (COLOMBIA AND VENEZUELA). *Spirochæta venezuelensis (neotropicalis).*
Animals susceptible.	Small rodents, only after passage through monkeys.	Gerbilles. Monkey (*Cercopithecus*).	Rats, field mice (*Microtus guentheri*).	Guinea-pigs, desert foxes, jackals, and Moroccan hedgehogs.	Small rodents and many animals susceptible.	Chipmunks (*Eutamias Sp.* Armadillo.	Rats and S. American monkeys, marmosets (*Leontocebus geoffroyi*), opossums (*Didelphys marsupialis*), armadilloes (*Dasypus novemcinctus fenestratus*).
Course in animals.	Mild.	Very mild.	Mild.	Severe.	Very severe.	Fairly severe.	Severe.
Subinoculations in animals.	Monkey to monkey, mouse to mouse. Persistent brain lesions.	Gerbille to gerbille.		Guinea-pig to guinea-pig.	Monkey to monkey. Positive. Shrew-mice (Crocidura) in Dakar. Brain infections.	White mice to mouse and squirrel.	Rat to rat. Slightly pathogenic.
Course in man.	2–4 relapses. Incubation period 2–10 days. Duration of attack 5–6. Apyrexia 7–10.	Fairly severe attack, usually short, average 2–6 days. Relapses 2–3, sometimes 7.	Apparently resembles foregoing.	Apparently resembles the Central African Form. Fairly severe with 4–6 relapses of 3–4 days each.	Severe: 5–11 relapses. Incubation period 7–10 days. Duration of first attack 3. Apyrexia 1–8. Complications severe.	Resembles Cosmopolitan form.	Resembles Central African form. Many cases benign.
Natural transmitters.	Lice (*Pediculus humanus*).	Ticks (*Ornithodorus papillipes (tholozani)*, (*O. lahorensis*)).	Ticks (*Ornithodorus papillipes (tholozani)*).	Ticks (*Ornithodorus erraticus, marocanus*).	Ticks (*Ornithodorus moubata, O. erraticus, O. savignyi*). Hereditary transmission.	Ticks (*Ornithodorus hermsi*).	Ticks (*Ornithodorus venezuelense, O. turicata, O. talaje*).
Serum reactions.	Immune serum not agglutinating *S. duttoni.*	Immune serum not agglutinating *S. recurrentis.*		Immune serum not agglutinating *S. recurrentis.*	Immune serum not agglutinating *S. recurrentis.*		Immune serum not agglutinating *S. duttoni.*

N.B.—In all tick-borne infections transmission is hereditary; this probably does not occur in the louse-borne disease

and now in California it has been described by Wheeler, Herms and Meyer.

Meleney has found that the grey squirrel (*Sciurotamias davidianus*) and the striped chipmunk (*Eutamias asiaticus*) could be experimentally infected with the Chinese strain of spirochæte. After splenectomy the virulence of the attacks in these animals was increased.

Pathology.—The spleen is usually large and soft, often shows multiple infarcts and fibrinous exudates, and may rupture spontaneously during life. Liver, kidneys, and heart show cloudy swelling of their cellular elements. The skin in fatal cases is usually jaundiced, and there may be subcutaneous petechiæ. The bone-marrow is hyperæmic, and shows great activity of the leucoblastic elements. There is generally a marked polymorphonuclear leucocytosis, and the spirochætes, very numerous, often phagocytosed, are found in the spleen and bone-marrow. In microscopical sections of the spleen and liver the spirochætes are seen in great numbers within the endothelial cells—an observation which suggests that the parasites retire to these organs during the apyrexial periods. They rapidly disappear after the patient's death. During the apyrexial periods an occasional one may be found in the peripheral blood by injecting intraperitoneally not less than 25 c.c. into a susceptible animal, which must be examined twice daily for the succeeding ten days before a negative result can be declared.

There are those who think that the spirochæte has an invisible stage in the blood. It is said that if a drop of blood containing few spirochætes is placed in sterile vaseline and incubated, it will in a few hours be found swarming with large numbers arising from forms previously invisible.

In Germany and Austria strains of relapsing fever spirochætes have been used for therapeutic inoculation in the same manner as malaria. Some facts of importance have emerged as the result of this study: that the spirochætes may be demonstrated in the liver, brain and cerebro-spinal fluid and that active infection may be produced by inoculation of susceptible animals with material obtained during the quiescent periods and even after apparent reovery from the disease.

Sagel has shown that infection produced by the bite of a tick is much more virulent than that brought about by direct inoculation. Pampana has shown that the relapsing-fever spirochætes are remarkably neurotropic and in guinea-pigs the brain and cerebellum are still infective fourteen months after primary inoculation. A great deal of attention has recently been paid to the fixation in the brain of these spirochætes, which takes place in the spirochætes of mice and birds. Similarly Mathis and Durieux show that strains of *S. duttoni*, originally isolated from shrew mice in Dakar, may persist in the brains of subinoculated mice up to 235 days.

Mode of transmission.—There are two main forms of intermediary host which transmit relapsing fever, namely lice and ticks. The form of fever as it occurs in Europe, Asia, and North America

is conveyed by lice (*Pediculus humanus*). The Iranian and Palestinian form, *S. persica*, is said to be transmitted by a tick, *O. papillipes*, formerly *O. tholozani*. Tick fever, the Central African form, is undoubtedly transmitted by another ornithodorus, *O. moubata* (Plate VII, Fig. 3), and in Senegal by *O. erraticus*. The analogous disease of Central and South America is conveyed by *O. venezuelensis* and *O. talaje*. According to de Buen, *O. marocanus* transmits relapsing fever in Spain and Morocco. In Turkestan, too, it is *O. papillipes*; in California, *O. hermsi*.

It is becoming increasingly realized that a reservoir of infection of these relapsing-fever spirochætes exists, especially in Africa, in the smaller rodents which, quite normally, appear to be infected with them. Nicolle and Anderson in Tunis recognize that the spirochæte of these mammals, *S. normandi*, is probably identical with *S. duttoni*. This group is virulent to rats and mice, but is not pathogenic to guinea-pigs. The *hispanica* strain is equally virulent to mice, rats and guinea-pigs.

Russell in Accra (Gold Coast) has found the pouched rat (*Cricetomys gambianus*) to be most susceptible to infection with *S. duttoni*. It is now generally admitted that the spirochæte of the shrew mouse, *S. crociduræ*, is identical with *S. duttoni*. In Panama, Clark and Dunn have found a wild squirrel monkey—*Leontocebus geoffroyi*—naturally infected with *Spirochæta venezuelensis*, which was proved to be transmissible to man.

Epidemiology and endemiology.—The fevers caused by *S. recurrentis* occur, as a rule, at definite seasons of the year, depending upon the circumstances which favour the propagation of their intermediary host, the body-louse. In times of peace the poorer and indigenous class of the community is attacked. In Europe, for instance, relapsing fever has been a feature of times of famine. This has long been noted in Ireland, where it is known as "famine fever," and during recent years widespread epidemics have occurred among the partially starved population of Central Russia. In war-time it is the scourge of armies in the field, and is commonly associated with epidemics of the dreaded typhus, itself also a louse-borne disease. The two infections may coexist, as was noted in the great Serbian epidemic of 1915. In Southern Europe and Northern Africa relapsing fever is a disease of the winter and spring months, at which time the natives are wont to envelop themselves in thicker clothes than usual and to congregate together for the sake of warmth, thus facilitating transmission. Considerable alarm was caused by the rapidly advancing and widespread epidemics of louse-borne relapsing fever which swept across Africa in 1921, starting from Upper Guinea and, according to Lasnet, probably introduced from the Mediterranean. In two years the number of deaths caused in the French Sudan and the Niger was estimated at 80,000–100,000. In the upper Volta area it caused 20,000 deaths, and in 1926 in Darfur it killed over 10,000 people. Generally speaking the louse-borne disease is uncommon in Equatorial Africa,

where, on account of the scantier clothing worn, this insect is unable to thrive. In Dakar and certain parts of Senegal, however, the infection is tick-borne and is said to be identical with *S. duttoni.* In India it has been noted that at the advent of the hot weather, in April and May, the lice die off and the epidemics of relapsing fever come abruptly to an end.

The tick-borne forms of relapsing fever differ considerably from the foregoing, in that the infection is transmitted hereditarily by these arthropods, and the infection is confined to houses and localities which afford a suitable environment for *Ornithodorus.* In Central Africa it has been known for many years that the "rest-houses" on the main routes of travel are endemic centres of tick fever, for the ticks live in the mud walls and roofs of the huts, and emerge at night-time to feed on man. There is therefore no seasonal incidence in this disease, as occurs in the other forms of relapsing fever. The same has been noted in the South American form, except that a greater incidence is observed in the wet and rainy season, when native labourers and oil prospectors are necessarily more confined to their quarters than during the finer months of the year.

Evolution of the parasite in the intermediary host.—Philip Ross, Milne, Dutton and Todd have definitely shown that *S. duttoni* is normally conveyed by the tick *O. moubata*, and that it can be transmitted, not only by the insect which has bitten the infected individual, but also by its progeny, even to the third generation (Koch): thus, as noted above, the spirochæte has actually been demonstrated within the eggs laid by infected ticks. From these eggs nymphs are produced in which the organism multiplies in large numbers. Once fed on spirochæte-containing blood, ticks remain infective for one and a half years, and can convey by successive bites relapsing-fever infection to at least ten monkeys.

Wheeler, Herms and Meyer found a new tick vector in California in *Ornithodorus hermsi*, which they collected from Lake Tahoe, Big Bear Lake, San Bernardino, Eldorado and Placer counties, at an elevation of 5,000–8,000 feet. These ticks were found naturally infected with the Californian strain of *S. recurrentis*, and produced infection in mice and monkeys on which they were fed. Chipmunks and squirrels which abound there are the reservoirs of infection. The bites of both male and female ticks in all instars are infective.

Development in the tick.—According to Leishman, the spirochætes remain motile for several days after ingestion by the tick (*O. moubata*), the duration depending upon the atmospheric temperature; they then lose their motility and break up into chromatic granules which clump together in the Malpighian tubules of the tick. Should the temperature be raised, a crop of young spirochætes develop from the granules and then disappear suddenly. It would appear that recurring multiplication of the spirochætes takes place in the tissues of the tick in much the same way as in man. The Malpighian tubes act in this

case as culture-tubes, the organisms being subsequently passed out in the fæces of the arthropod. The entrance of the spirochæte into the human skin is aided by the irritation caused by the bite, which provokes scratching and consequent inoculation of the deposited spirochætes; this is facilitated by the fluid exuded from the tick's coxal glands which acts as a diluent. According to Nicolle and his co-workers, *S. duttoni* cannot be transmitted by lice. Other observers do not agree that the development proceeds in the exact manner

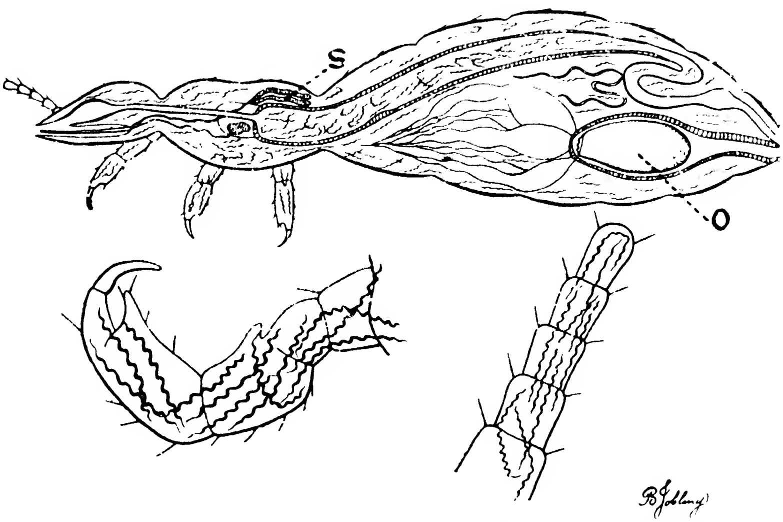


Fig. 33.—*Spirochæta recurrentis* **of relapsing fever, and its development in louse** (*Pediculus humanus*). (*C. M. Wenyon,* "*Trans. Roy. Inst. of Gt. Brit.*")

Diagram shows whole body invaded by spirochætes. S, salivary glands; O, egg. Below, spirochætes in leg and antenna, which are easily broken off, so that fluid exuding from body infects skin of host.

described above, but regard it as identical with the developmental stages seen in the louse.

There has been controversy as to the meaning of the chromatic granules seen within the body of the tick, but it is probable that these are of two kinds, some representing a degeneration of the defunct spirochætes, while others are to be regarded as active stages in the developmental cycle of the organism. The fact remains that for a considerable time after ingestiont fully-formed spirochætes cannot be demonstrated within the body-cavity of the infected tick. Wenyon states that the granule stage of the parasite in the tick has not been definitely proved.

Development of the parasite in the louse.—The spirochætes in the stomach of the louse alter very rapidly, and disappear within twenty-four hours at a temperature of 73° F. The so-called "metacyclic" organisms appear in great numbers on the sixteenth day in the body-

cavity ; at the end of this time the organisms are more slender and, as a rule, shorter than those found in the blood, but they develop to their full size in a few days' time (Fig. 33). Thus it has been proved that the lice become infective on the sixteenth day, and the infection is probably conveyed by the fæces of the louse, or by the actual crushing of the insect on the excoriated skin. The infection may also be conveyed on the fingers and gain entrance through the conjunctiva. Under optimum conditions, 43 per cent. of lice become infective and remain so for twenty-eight days. There is no conclusive evidence of hereditary transmission in this insect. The body-louse (*P. humanus*) lays on an average 75 eggs each in the clothes of its host, and these hatch in four days and become adult and fecund in two weeks.

Other methods of transmission.—The spirochætes have been proved to be capable of penetrating the mucous membrane and, if well rubbed in, the unbroken skin. Nurses and doctors engaged in treating relapsing-fever patients have been inoculated with the disease through the entry of infected blood into the conjunctival sac, and in the case of pregnant women and experimental animals it has been proved that the organism can pass through the placenta to the fœtus.

White mice and white rats are especially susceptible, the former particularly so, the organisms appearing in the blood within twenty-four hours of inoculation and persisting to the third day. About this time they disappear for several days from the blood until the commencement of the first relapse, which may be followed by a second, third, or even a fourth, the number varying in individual mice ; with each relapse the parasites reappear in the blood. The interval between the relapses is generally about seven days ; occasionally it is only two, though it may be as many as ten. The actual number of organisms in the blood in the first is greater than in subsequent relapses, indicating the development of a partial immunity. Recovery in mice is the rule.

As a result of the consecutive passage of the spirochæte through a long series of rats, its virulence is augmented, so that the incubation period becomes reduced to 15–18 hours, and the persistence of the parasite in the blood is prolonged to 60 hours instead of, as originally, 48 hours ; at the same time the spirochætes become far more abundant.

Emerson, Mossman, Beunders, Rothermundt and others have shown that the spirochæte has a definite neurotropic tendency, and that after subinoculation of *S. duttoni* in mice a residual brain infection is produced.

In rats an acquired immunity may be produced which lasts for many months. As a rule, *S. duttoni* produces a far more severe disease in these animals than does *S. recurrentis*.

Rabbits and guinea-pigs are relatively refractory.

As regards *S. venezuelensis*, dogs, rats and guinea-pigs are

refractory. Man and certain squirrel monkeys appear to be the chief reservoir of the virus. Mice which have been rendered immune to *S. duttoni* are subsequently capable of being infected by this spirochæte.

Immunity.—Sabritschewsky, in 1896, showed that when equal parts of spirochæte-infected blood or serum and normal serum are mixed, the spirochætes survive longer than when the infected blood is mixed with that of a patient who has recovered from relapsing fever. He accordingly concluded that the cause of the crisis in relapsing fever and of subsequent immunity was the development of a germicidal substance in the blood. He was the first to apply serum-therapy in the treatment of relapsing fever, and obtained an anti-spirochæte serum by repeated inoculation of the horse with human spirochæte-containing blood. The value of this was successfully established by Löwenthal; of 87 patients treated, 43 (49 per cent.) recovered without a relapse.

Treated *in vitro* with hyper-immune serum, the spirochætes rapidly become unrecognizable aggregations of granules, and this phenomenon may be manifest in a dilution of 1 : 2000.

Cunningham in 1925 showed that the spirochætes which are found in the blood in the initial attack differ serologically from those which bring about the first relapse, and these strains on inoculation into animals maintain the same characteristics. Thus, if strain A be inoculated into an experimental squirrel, the initial attack will be of that serological strain, but in the subsequent relapse the strain will be B; but if the B strain be inoculated, the relapse will be A, and so on. There is thus an alternation of serological strains. It is probable that the antibodies produced in the blood-stream by one particular strain do not persist long enough to prevent relapse from taking place. The thrombocytobarin, or adhesion phenomenon, shows clearly that serological differences exist between the spirochætes of the first attack and those of the second.

General Symptoms Common To All Forms

1. Cosmopolitan type (*Spirochæta recurrentis*).—The course and character of the disease vary greatly in a single epidemic, and, further, the virulence of the more severe forms is much greater in some outbreaks than in others. The *incubation period* usually lasts from two to ten days. In some instances the attack develops promptly on exposure; it is never delayed beyond the fourteenth day. In the artificially inoculated, symptoms show themselves in from two to six days.

The *onset* is generally abrupt, being characterized by chilliness or rigor, giddiness, epistaxis, vomiting, photophobia, and intense headache. In the young there may be convulsions. Temperature rises rapidly to 104° or 105° F., sometimes to 108° (Chart 8). The pulse is rapid, 110 to 130. Should fever run high, there may be delirium. The skin is dry, although, especially during the first day, occasional sweats may break out. A slight icteric tinting of the conjunctiva is usual, and not infrequently jaundice is marked at the crisis. The spleen is invariably enlarged and tender. The tongue

is coated and moist, except in bad cases, in which it may become dry and brown. The bowels, as a rule, are confined; abdominal pain may be considerable, and patients usually complain of pains in the muscles of the legs, especially the calves. Occasionally herpes labialis is noted. There quite commonly occurs an erythematous rash in the initial fever, and later one of rose-coloured spots on the trunk and limbs has been observed; some authors describe petechiæ. The rash has a peculiar distribution, being generally most marked in the region round the neck, spreading in a semicircular fashion from the tips of the mastoid processes; thence it ranges in a symmetrical manner round the shoulders, down the sides of the chest and abdomen to the inner aspect of the thighs, and to the extensor and flexor aspects of the forearms. The individual petechiæ may be as large as a threepenny bit, and need to be carefully differentiated from the exanthemata of typhus and hæmorrhagic smallpox.

The primary remittent fever, may last from five to seven days. At first the morning is usually lower than the evening temperature, but on or about the third day the evening temperature rarely rises above that of the morning. On the fourth, fifth, or sixth day there is again a rise of temperature, sometimes with delirium, ending in a crisis of profuse sweating and diarrhœa. The temperature now falls rapidly to normal or subnormal, sometimes dropping in the course of a few hours as much as 12° F.; in the latter event, especially in elderly or delicate patients, there may be dangerous collapse.

The initial pyrexia, called *first paroxysm*, is followed by a *first period of apyrexia* during which the patient recovers so rapidly that after four or five days it may be difficult to keep him in hospital. But from seven to nine days after the crisis, that is about the fourteenth from the commencement of the attack, rigor again occurs, followed by a second attack of fever—*first relapse*. This may be more severe than the initial paroxysm; usually it is milder, and seldom lasts so long. During its continuance the secretion of urine is considerably increased; sweating also is profuse, and prostration marked. A polymorphonuclear leucocytosis of 15,000 and over is found during the pyrexial periods.

With the defervescence of the first relapse the patient enters on the *second period of apyrexia*, which is usually coincident with convalescence (Chart 8). But in some patients a *second relapse* may occur, usually about the twenty-first day, counting from the commencement of symptoms. This second relapse rarely lasts longer than three days, and is generally milder than the previous paroxysms. In rare instances three, four, five or even more relapses have been observed. Anomalous types of fever are common. Some temperature charts show an intermittent fever throughout, more resembling that of phthisis than anything. Cases with four relapses in a period of twenty-six days are met with. Occasionally the apyrexia period may be of considerable length—seventeen days; in one case observed,

forty-two days. In some epidemics chronic diarrhœa, in others arthritis, is a feature.

Convalescence may be protracted, and complicated with such sequelæ as nephritis, ophthalmia, iritis, œdema of the eyelids, otorrhœa, polyarthritis, pneumonia, neuritis, parotitis, adenitis. In pregnant women abortion is the rule. In some cases attacks of abdominal pain are noted which resemble appendicitis.

Bilious typhoid form.—This is thought by some to be a distinct disease and on account of the severity of its symptoms and rapidity of its course, especially on the West Coast of Africa, is apt to be mistaken for yellow fever. In addition to high fever, dyspnœa, intense jaundice,

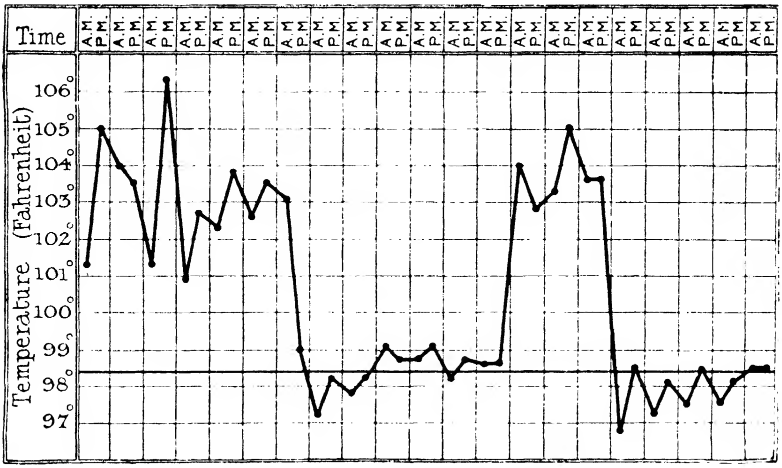


Chart 8.—Relapsing fever, cosmopolitan type. (*Orig.*)

and enlargement of the spleen are noted. Hæmorrhages into the skin and from the internal organs commonly occur; marked albuminuria is the rule.

Some cases become stuporose, with development of tympanites, hiccough, and severe diarrhœa. These severe forms are more generally seen in war-time, when, in the presence of starvation and exhaustion, the disease assumes a more serious aspect.

II. Iranian type (mianeh disease) (*Spirochæta persica*).—This type is said to be due to the *S. persica*. It is found throughout Iran, apparently also in Syria and in Northern Palestine. The symptoms may be said to be intermediate between those of the European and those of the Central African type, for, as compared with the European, the relapses are more numerous and of shorter duration, while the organisms are very scanty in the peripheral blood, requiring a thick-drop method for their demonstration (Chart 9). The attack

is generally a very mild one; the initial pyrexia shows marked morning intermissions, and lasts four to five days, when the temperature comes down either by lysis or by crisis. Three, four, five or even more relapses are often noted, individual relapses lasting sometimes only twenty-four hours, or, at a maximum, three days. The spleen is rarely enlarged, and icterus does not occur as a rule. According to Harold, in certain epidemics the disease may assume a more severe aspect, jaundice and other complications may supervene, and the mortality may be high.

III. Central African type (carapata disease; tick fever) (*Spirochæta duttoni*).—The African tick-conveyed spirillum fever, caused by *S. duttoni*, although, as regards the type of fever, resembling

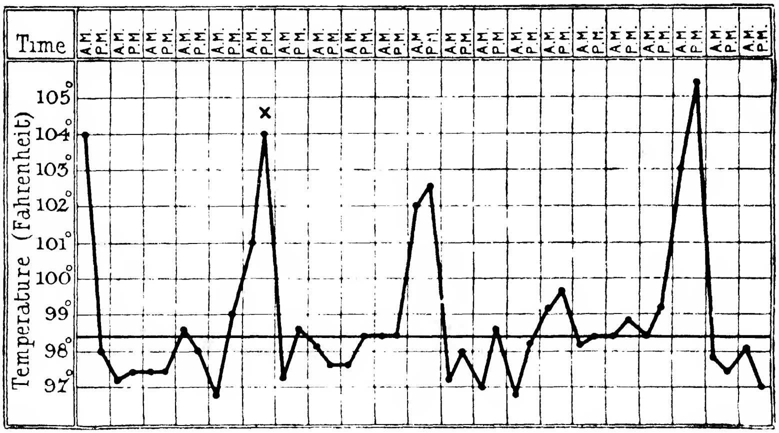


Chart 9.—Relapsing fever, Iranian type. (*Bellingham Smith.*)
x Spirochætes demonstrated in blood-film.

the classical European and Indian forms, differs from these in some important particulars. The initial fever is not usually so prolonged, generally terminating by crisis within three days. Diarrhœa and dysenteric symptoms are not uncommon. The apyretic intervals are of very irregular duration, being, according to Philip Ross, sometimes as short as one day, sometimes as long as three weeks; and instead of only one or two relapses, as in ordinary relapsing fever, there may be as many as eleven, five or six relapses being the rule (Chart 10). The fever, though shorter, is as severe in the relapses as in the initial paroxysm, but the intervals tend to become longer. In some instances the reverse is the case, and this perhaps in both particulars. Sometimes the fever may assume a low chronic form, it may be with severe headache and vomiting. Iritis is a not uncommon complication or sequela. The liver and spleen are generally enlarged, and bronchitis and pneumonia are frequent complications. As already

stated, the parasites are usually very scanty in peripheral blood, and may be hard to find. There is a polymorphonuclear leucocytosis, as in the European type, and a slight anæmia of the aplastic type.

Fulminating cases, in which the onset is very sudden, were observed nine times in a study of 1,500 cases during the East African campaign by J. K. Manson and Thornton. In these the spirochætes occur in enormous numbers; coma and death may ensue within twenty-four hours. Sometimes there is most intense icterus. These observers considered that death is brought about by the impaction of masses of spirochætes in the cerebral capillaries.

In natives of the endemic districts the disease, as generally observed is not nearly so severe as in Europeans and strangers, being usuall, limited to a paroxysm or two of one or two days' duration. Thy

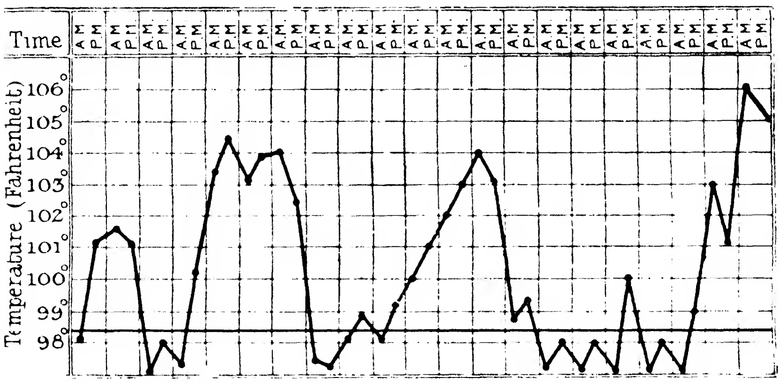


Chart 10.—Relapsing fever, Central African type. (*Newham.*)

mildness of these attacks is probably explained by a partial immunity conferred by previous attacks.

Implication of the central nervous system is a not uncommon complication. A particularly distressing, but fortunately somewhat rare, complication is optic atrophy. In the Editor's experience there are two forms—one which follows immediately upon the cessation of the fever, and another which gradually develops several months afterwards. The neurotropic tendencies of the spirochætes have already been referred to. Some observers have described aphasia, facial paralysia hemiplegia, and implication of the cranial nerves—such as the third, fourth, and sixth (resulting in ptosis and strabismus), the fifth (trigeminal neuragia), the seventh (facial paralysis), and the eighth (deafness)—as coming on suddenly during the course of the disease. In these nervous complications the spirochætes may sometimes be demonstrated in the cerebro-spinal fluid; as a rule, it contains an excess of lymphocytes and is under considerable pressure,

necessitating lumbar puncture in order to relieve symptoms. In patients infected with subtertian malaria a superimposed attack of relapsing fever may determine the onset of blackwater fever. Iritis and irido-cyclitis, either unilateral or bilateral, are frequent accompaniments of the acute stage and may precede the optic atrophy already referred to. Arthritis is a not uncommon complication.

IV. Spanish type (*Spirochæta hispanica*).—The most complete study of the clinical aspects of this form of relapsing fever is by Más de Ayala (1931). The incubation period is apparently a very short one, 1–2 days, and the onset of the fever is abrupt. It is ushered in with nausea, headache, chilliness, general malaise, a rise of temperature to 40° C. (104° F.) with congestion of the face and eyes, and dryness of the mouth and lips.

The *initial pyrexia* persists for 3–4 days and is associated with drowsiness and prostration, and usually with enlargement of the spleen. There is the usual rapid fall of temperature at the crisis, often associated with collapse which responds to injections of adrenalin.

The periods of apyrexia and relapse correspond closely to those of the Central African form. After four attacks the disease apparently comes to an end spontaneously. The Spanish form of relapsing fever does not seem to be associated with a secondary anæmia as in the other forms, though there is generally a leucocytosis of 14,000 to 26,000 per c.cm. during the attacks. Herpes labialis is common and the urine often contains bile at the crisis. In this form enlargement of the cervical lymphatic glands is said to occur.

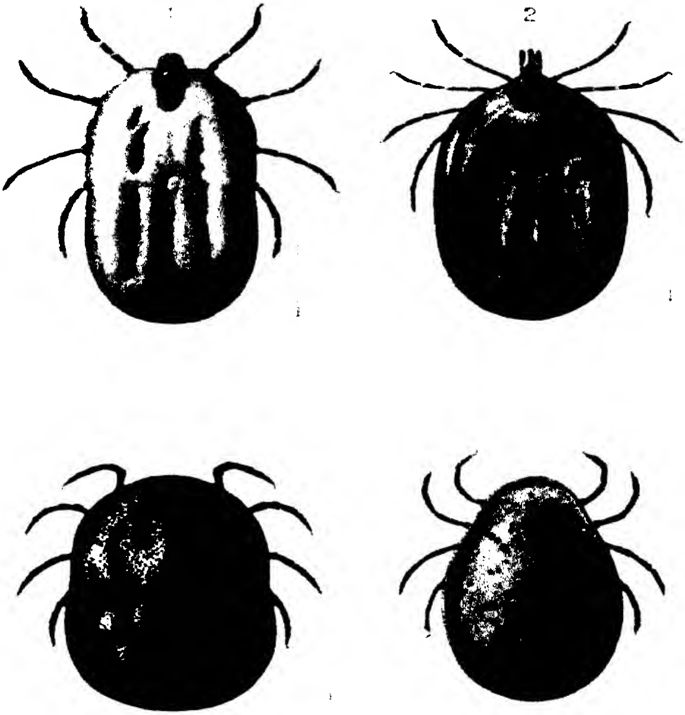
As in *S. duttoni* infections, nerve complications have, though rarely, been noted. Facial paralysis has been seen in about 3 per cent. some six weeks after the last relapse, and in about the same proportion of cases iritis is noted.

The prognosis is usually good and the pyrexia can generally be cut short by neosalvarsan injections. The immunity to this strain of spirochæte appears to last about a year.

V. Central and South American type (*Spirochæta venezuelensis*).—As far as is known, this fever resembles in almost every particular the Central African form described above.

Mortality of relapsing fever.—The death-rate is usually below 6 per cent. In a serious form with jaundice, which has been noticed on the West Coast of Africa, the death-rate may exceed 50 per cent. In the feeble and old, death may ensue at the height of the first paroxysm, or from exhaustion as the result of relapses.

Diagnosis.—This fever is most usually confounded with subtertian malaria, from which it may be indistinguishable on clinical grounds; it may also resemble infectious jaundice, enteric, typhus, influenza, dengue, pneumonia, malignant smallpox, and even plague In South America and West Africa it may be confused with yellow fever. The detection of the spirochætes with the microscope, or by animal inocu-



1, *Margaropus (Boophilus) annulatus* **(partially distended). 2,** *Ixodes reduvius* **(partially distended). 3,** *Ornithodorus moubata* **4,** *Argas persicus*.

FEMALE TICKS.

PLATE VII

3

1. **Rash of trypanosomiasis.** (*T. gambiense.*) (*Dr. F. Murgatroyd.*)

1 (a.). **Primary lesion, site of infecting tsetse bite on leg.**

2. **Dengue rash** (*after Cleland, Bradley and MacDonald.*)

3. **Rash of fièvre boutonneuse** (*typhus*) **on legs** (*after D. and J. Olmer*, 1933.)

RASHES.

PLATE VIII

lation, is the most reliable method of diagnosis. They are readily demonstrated with the dark-ground illumination; for methods of staining, *see* p. 1023. At an early stage the relapsing character of the fever is not available as an aid to diagnosis, but at a later period the history of a fever which had relapsed about fourteen days from the onset of the disease should be regarded as highly suggestive.

Wassermann reaction.—A strong positive complement-deviation is obtainable, both during the pyrexial stage and in the apyretic periods between the early relapses, in about 20 per cent. of cases. This apparently applies to all clinical types of the disease and therefore does not necessarily indicate a syphilitic infection.

Treatment.—Careful nursing and dieting are necessary, especially in the African type, and must be maintained after the crisis, when the patient is ravenously hungry.

(1) *Salvarsan.*—In salvarsan and its allied preparations we have a specific. The one selected should be given by the intravenous route in doses of 0·3 grm. to 0·9 grm., according to the age of the patient and the severity of the case, the dosage being reckoned as 0·01 grm. for each kilogram of body-weight. After a short aggravation of symptoms a crisis takes place with the disappearance of the spirochætes from the blood, and, in the vast majority of cases, recovery. Should relapse occur—a rare event—a second injection may be given. Of the salvarsan (arsphenamine) compounds, undoubtedly novarsenobillon is the best; neosalvarsan, luargol, arsalyl, kharsivan, galyl (0·35 grm.), and salvarsan are useful in a descending order of merit, and recently sulphoxyl-salvarsan (Höchst) has given good results. The last mentioned, as also sulphostab (Boots), in doses ranging from 0·3 to 0·6 grm., has the additional advantage that it may be given by the intramuscular or deep subcutaneous routes. Evidence shows that the drug is most efficacious when given in the pre-critical period—that is, when the temperature is on the rise, directly the diagnosis has been made: relapses are apt to occur if given while the temperature is *on the fall*, or during the apyretic period; this is especially true of the Central African type, some cases of which appear to be specially resistant to salvarsan treatment. If it is not given in the first attack, one should wait till the first relapse, and then give it on the rise of temperature. Salvarsan ought not to be injected when the crisis is imminent: a very grave reaction, due to the great destruction of the spirochætes and the liberation of their toxins, with corresponding aggravation of the symptoms and, it may be, fatal collapse, is apt to ensue. On the other hand, the great majority of otherwise healthy patients recover from most forms of relapsing fever without specific treatment at all, although, on account of relapses, convalescence may be prolonged. Albuminuria should not constitute a contraindication to salvarsan treatment.

Apparently arsenic-resistance is rapidly acquired by these spirochætes.

so that Moretti and others who have studied this problem find that arsenical compounds, which are efficacious in the earlier stages of relapsing fever, may be ineffectual if a prolonged period (say of 100 days) is allowed to elapse between the experimental infection with the spirochæte and the giving of the drug.

(2) *Stovarsol, or spirocid* (van Hoof).—Stovarsol tablets (4 gr.) in doses of six daily are said to be singularly efficacious in relapsing fever, when, for some reason or other, intravenous injections cannot be undertaken.

(3) *Other compounds.*—It has been claimed in Tanganyika that in *duttoni* infections intravenous injections (20 c.c. of a 1-per-cent. solution) of mercurochrome are more beneficial than salvarsan. Recently gold compounds have been advocated by German workers—Solganal B and A.69, the former of which contains 36.5 per cent. of gold. It is claimed that residual infections in the central nervous system are eliminated by these preparations. Both preparations may be given intravenously or intramuscularly. As the result of experiments in mice, Menk has advocated the combined treatment with solganal and neosalvarsan—a mixture of half the tolerated dose of the former and about a third the dose of the latter being necessary.

(4) *Other methods.*—The collapse and fall of blood-pressure with subnormal temperature which follow the crisis have to be counteracted by strychnine, brandy and intrarectal douches of hot salines, and also by injections of adrenalin and ephedrine.

Prophylaxis.—In the louse-conveyed forms of relapsing fever, prophylactic measures are necessarily aimed at the destruction of lice and their eggs by all the measures known to sanitary science—often a matter of very considerable difficulty when dealing with large groups of native porters or labourers, especially during the rainy season. This disinfestation is best performed by means of superheated steam in a portable Thresh's disinfector, or in specially constructed cars in a disinfecting train, the superheated steam being supplied by the locomotive (Stammers). As head lice can convey relapsing fever in the same manner as the body pediculus, local measures, such as application of *oil of sassafras* to the head, must be undertaken.

In the African form, prophylactic measures are much more difficult, and necessitate an intimate knowledge of the habits of Ornithodorus, which does not live on the body of its victim, but emerges at night-time from the native houses to feed on blood. It is also found on the veld living in the burrows of the wart-hog, but as a rule it is only met with in numbers in the vicinity of old camping sites (*see* pp. 973–974). The ornithodorus itself is very difficult to destroy, and may remain uninjured after prolonged soaking in cresol.

The following rules are necessary:

1. Avoidance of native houses, most of all at night-time—especially those situated on much-frequented routes

of travel. Bedsteads of native manufacture should also be avoided. Camps should be placed as far distant as possible from native villages.

2. Avoidance of much-frequented ground for camping sites; it must be remembered that Ornithodorus can exist without food for years. Sleeping on the ground should not be practised unless absolutely necessary, and only when well protected by a mosquito-net. The use of a night-light is recommended to scare away the ticks. Blankets should be carefully inspected before retiring to rest.

Native huts should be so constructed that a space of 8–10 in. intervenes between the walls and the ground. Mud and rubble buildings are inadvisable; floors should be raised, and made of cement. A deep trench dug round a building and filled with wood-ash has been found effective in excluding ticks.

Children especially act as a reservoir of the virus, and the ticks feed upon them.

Prophylactic inoculation.—Attempts to artificially immunize the inhabitants of an infected district have been undertaken by Russian workers with a vaccine composed of a mixture of cultures of the original and relapse strains of *S. recurrentis*, which had been incubated at 37° C. for three days and subsequently kept at room temperature for 14–16 days until they had lost their virulence. Each man received 1·0, 1·5, and 2·0 c.c. at three days' interval. A week after the last injection the blood was found to contain spirochætolysins against both original and relapse strain. The results showed that it was possible to produce immunity by inoculation of dead spirochætes.

For a description of the ticks (Plate VII) and their habits, *see* p. 973.

CHAPTER VII

LEPTOSPIROSIS

DURING recent years it has become possible, through the discovery that certain delicate spirochætes (leptospiræ) are present in the blood-stream and in various viscera, to group together certain fevers which have certain clinical features in common. Under the heading of Leptospirosis are included infectious jaundice and seven-day fever, and possibly certain less well-defined types.

INFECTIOUS JAUNDICE

Synonyms.—Weil's Disease; Icterus Gravis; Spirochætosis Icterohæmorrhagica; Mediterranean Yellow Fever; Griesinger's Disease; Odan-eki (Japanese).

Definition.—A severe form of fever, especially in sewer workers, caused by *Leptospira icterohæmorrhagiæ*, associated, though not invariably, with jaundice, enlargement of the liver and sometimes of the spleen. The natural reservoir of infection would appear to be the rat (*Rattus rattus* and *R. norvegicus*).

History.—An acute febrile illness associated with jaundice and a high mortality was first described by Weil in 1886, and has since been known as Weil's disease. In 1915 Inada, Ido, and other Japanese investigators described the spirochæte *L. icterohæmorrhagiæ* as the cause of the disease, and this was confirmed in Germany by Huebener and Reiter in the same year. In the early summer of 1916 this disease occurred sporadically among the allied and German troops in France, and the Japanese discovery was soon confirmed by Stokes, Ryle, and Tytler among British troops, and by Uhlenhuth and Fromme on the German side, while Bonini recognized it on the Italian front. In 1917 the same Japanese investigators, by means of guinea-pig inoculations, proved the presence of the leptospira in otherwise healthy rats (*R. norvegicus* and *R. alexandrinus*) and in the field-vole (*Microtus montebelloi*).

Geographical distribution.—The disease appears to be especially prevalent in Japan; during the Great War, outbreaks occurred among the troops in Gallipoli and Salonika, and also in Egypt, where the disease had long been known to exist. It is found along the North African coast and the shores of the Mediterranean. It is known to occur in France, Italy, Germany, Holland, the United States, Peru, Brazil, and Buenos Aires, and is endemic in West Africa, the Congo, and the Sudan. Epidemics have been described in the Andaman

Islands and in the Malay States (Fletcher). The form of the disease as it occurs in the tropics is said to be more virulent, though further researches on this point, as well as on its distribution in hot countries, are necessary. In Europe it is said to be more common in summer-time, especially in Holland, where Schüffner has observed 451 cases in the last ten years. The disease is specially prevalent in South Holland and in the city of Rotterdam. The Editor, in 1922, recorded a case in London; others have been observed in Scottish coal-mines (Buchanan), and in Aberdeen. In 1934 it was shown that Weil's disease is by no means uncommon in the sewer workers of London, and this work was soon confirmed by others who have found it in Liverpool and other cities, and also in persons engaged on canal work.

Epidemiology and endemiology.—In Japan the disease has a definite seasonal incidence, occurring, as a rule, most frequently in the months of September to November. In Europe it occurs most often in the hot summer months. The organism is found as a harmless parasite in the kidneys of wild rats and mice, and is excreted in their urine; and the disease is usually endemic among farmers and miners who are exposed to wet soil and water conditions, such as prevailed in the trench warfare and caused the epidemics of 1916 and 1917 in France. In the Andamans, epidemic jaundice is prevalent during the South-West Monsoon, and the cases are confined to adult males engaged in outdoor occupations.

In some cases water appears to constitute the source of infection, and epidemics have been recorded as occurring among soldiers in Italy and in Germany after bathing in certain river pools, and the Editor (1922) originally showed that polluted Thames water might be the source of infection. It is now known that spirochætes of the leptospira type are widely distributed in water, and some of them have been proved to be pathogenic on inoculation into guinea-pigs (Zuelzer).

In Holland Schüffner has shown that the highest incidence is amongst those people whose occupation leads them near water, and especially those who have fallen into it by accident. When the accident occurs in clean water there is no danger, but only in polluted canals.

Schüffner has now shown that the non-pathogenic *L. biflexa* (Zuelzer) occurs in any type of water, but that the presence of the pathogenic *L. icterohæmorrhagiæ* can be ascertained by immersing experimental guinea-pigs into suspected water.

Slime fever is the term applied to an abortive form of Weil's disease prevalent in Germany, where it is acquired during bathing in several districts. No less than 700 cases were reported in July, 1926. The attack begins with a rigor and a rise of temperature to 104° F. Accidental inoculation through the conjunctival sac has been observed.

Annual outbreaks of great severity of leptospirosis have been reported in 1933 and 1934 in Queensland. They have occurred among the sugar-cane cutters and farmers, especially after a prolonged rainfall, the infection having entered through scarifications of arms

and legs; a native species of rat (*Rattus culmorum*) appears to be the carrier of the infection. In 1934, Davidson, Campbell, Rae and Smith described an epidemic of nineteen cases in Aberdeen, chiefly among fish workers. The patients were employed in handling white fish in rat-infested premises the floors of which become covered with slime and offal. The skin of the hands is traumatized in doing this work, so that the infection can enter. Depilated guinea-pigs were easily infected with water obtained from this source. Weil's disease has, therefore, definitely become an "occupational disease."

The disease occurs in dogs, especially hounds, in which it is known as "the yellows," and it has been recognized in the fox and in leopards, especially when fed on rats.

Ætiology.—*L. icterohæmorrhagiæ* is found in the blood, urine, cerebro-spinal fluid, and sputum. It is a spiral filament with wide flexures, the individual spirals being in close apposition (Fig. 34). The largest forms attain a size of 20 μ by 0·25 , the average length being 6–12 μ.

It is now generally agreed that the organism is identical with *L. icteroides*, the organism originally described by Noguchi in yellow fever.

The organism may be demonstrated by the dark-ground illumination, but is so extremely active that its movements can only be detected with difficulty. According to Fletcher, they are most readily demonstrated in blood-films by Fontana's method. Although easily found in the blood of guinea-pigs, they can be found in man only with great difficulty. In microscopic sections of infected organs the leptospiræ show up well with Levaditi's method of silver-nitrate impregnation.

The organisms exhibit rapid movements: when free, one end is extended and straight, the other semicircularly hooked, so that they progress in the direction of the straight portion and appear to be propelled from the rear by the rotating hook.

This parasite has been cultivated by Noguchi on solid media such as blood-agar or gelatin (*see* p. 1040). According to Fletcher, the organism grows readily on agar impregnated with immune serum, but is agglutinated thereby in a peculiar manner. The culture medium used by Dutch workers consists of tap-water 1,500 c.c., Witte's peptone 0·15 grm., Ringer's solution 300 c.c., and Sørensen's solution *p*H 7·2. The final reaction of this peptone medium should be between *p*H 6·8 and *p*H 7·2. Three cubic centimetres of this medium is placed in a small tube and sterilized, and for use 3 c.c. of rabbit's serum is added. The tubes are then heated to 56° C. for thirty minutes and incubated at 37° C. overnight. Leptospiræ are seen by the dark-ground illumination by the fifth or sixth day.

According to Fletcher and Brown, there are distinct serological races of *L. icterohæmorrhagiæ*, the Andaman, Indian, and Sumatran strains being distinguishable from those found in Europe and elsewhere.

Schüffner now distinguishes a dog strain, *L. canicola*, which occupies a position analogous to that of *L. hebdomadis* and which is only found in Holland. *L. grippo-typhosa* is the name applied to the agent of "swamp fever" in Eastern Europe (Kosthaff).

Fletcher and his staff in Kuala Lumpur found that the organisms isolated from 26 patients could be separated serologically into six groups, whilst Baermann and Smits in Sumatra have studied nearly 400 cases. The symptoms of this form are mild and much more closely resemble a benign form of relapsing fever. The febrile periods last from 2–4 days.

Again, the strains of organisms isolated in Queensland by Clayton and Derrick differ from those of European origin and more closely resemble the Sumatran types. They have provisionally named them *Australis A* and *B*; the latter is closely related to *L. canicola*.

The natural reservoir of the leptospira appears to be the rat, in which it occurs in the fæces, urine, and kidneys, though it has not yet been demonstrated in the blood. It is believed that the disease was originally epizootic in rats, but that these animals have now become tolerant. The leptospira has been demonstrated in 32·4 per cent. of wild rats in Japan; to a less degree in France, Tunis, and

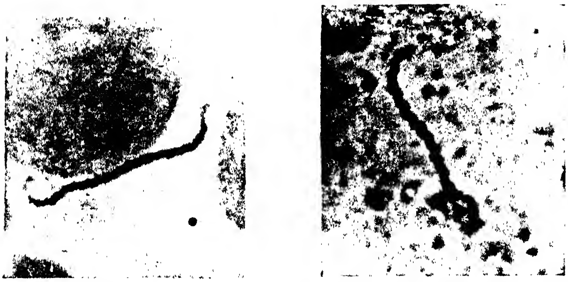


Fig. 34.—Photomicro of *Leptospira icterohæmorrhagiæ* from kidney of rat. × 3,000. (*Dr. A. C. Coles.*)

Algiers; and in 4 per cent. of sewer-rats in London (Foulerton). *L. icterohæmorrhagiæ* has been demonstrated by Buchanan in the zooglœa-like "roof-slime," which thus constitutes the source of infection in certain coal-mines in Scotland; and in the green slime of sewers in London by J. M. Alston. Probably the portal of entry is through skin abrasions, and guinea-pigs have been infected by rubbing in cultures, as well as slime or suspected water, through the depilated skin. Water is probably the main source of infection, especially when it comes into contact with the bronchial epithelium as by diving and swimming the "crawl stroke" (Schüffner). In Sumatra it is thought that the native dogs may constitute a reservoir, as Kowenaar and Wolf have found 6 per cent. of normal dogs in Medan to be carriers of the infection and the organisms have been proved to be present in the kidney tissues of normal dogs (*see* above).

Guinea-pigs are very susceptible to experimental infection, and so, also, but to a less degree, are dogs and puppies, rabbits and monkeys. In order to reproduce the disease in these animals, 3–5 c.c. of the

patient's blood are required, and should be injected intraperitoneally, when the animal dies of intense jaundice about the tenth day.

Pathology.—The liver is invariably increased in size, and may weigh 100–150 oz. The gall-bladder is generally half-filled with brown or greenish-brown bile; no blockade of the biliary ducts has been ascertained. The various microscopic lesions are reducible to three main types. In the first there is little destruction of the parenchyma or intercellular tissue; the second is characterized by extreme cellular degeneration; in the third there is a localized destruction of glandular tissue. The fatty degeneration of the liver in Weil's disease is moderate in degree, but cannot compare with that seen in acute yellow atrophy. The leptospiræ can be demonstrated in large numbers by Levaditi's method among the secretory cells of this organ. The spleen may be enlarged and the glandular substance soft and diffluent (about 12 oz.). A generalized enlargement of the lymphatic glands, especially at the hilum of the liver, with hyperplasia and multiplication of the mononuclear cells, has been noted. Hæmorrhages occur in the kidneys, mostly in the intertubular tissues; later in the disease the microscopic picture may resemble that of early interstitial nephritis, and the leptospiræ may be demonstrated in great profusion. The bone-marrow exhibits considerable changes, proliferation of the myelocytes, deposition of pigment in the macrophage cells, and diminished activity of the hæmopöietic system being the chief features. There are submucous petechiæ in stomach and duodenum, and hæmorrhagic patches in the lungs. The number of the red blood-corpuscles is diminished to about three million per c.mm., with a corresponding reduction in the hæmoglobin. There is said to be an enormous reduction in the number of blood-platelets to 10,000 per c.mm. (normally 200,000); the coagulation-time of the blood is increased to twenty minutes.

Inoculated guinea-pigs and puppies show in a marked degree the tendency to hæmorrhage; those occurring into the lung impart a characteristic appearance to that organ, the so-called "butterfly lung," or "butterfly patches."

Symptoms.—The *incubation period* in man, as well as in experimental animals, is from five to six days. In man the *onset* is acute, with rigors, vomiting, headache, diarrhœa, and abdominal pains. A few hours later, fever ensues, with thirst and an intense general aching of the limbs. There is intense injection of the eyes, which may constitute the earliest and most striking feature and which is almost pathognomonic and presents a distinct network of vessels on the cornea and sclerotics. It is believed that this reaction is due to primary invasion of the conjunctiva by leptospiræ. There is also a red plush-like injection of the soft palate. The intense prostration, the almost agonizing muscular pains and aching of the bones with hyperæsthesia of the calf muscles, constitute the most distressing features of the illness. The pyrexia is of an irregular type, between 103° and 105° F., falling by lysis in severe cases about the tenth or eleventh day. There is usually a secondary terminal rise of temperature lasting three to nine days, which is associated with the excretion of leptospiræ from the urinary tubules. Convalescence is established in the third week, but there is sometimes a short temporary recrudescence

of fever which is said to be an allergic phenomenon. Jaundice, which occurs in 50 per cent. of cases, is noted in from forty-eight to seventy-two hours from the onset, and may be ushered in by hæmorrhages into the conjunctivæ or skin, or even from the mucous surfaces. The skin is lemon- or orange-coloured, rarely greenish, pruritus being very frequent. Later, rashes which may be morbilliform, erythematous, or papular may appear; a purpuric rash betokens a bad prognosis. Herpes labialis, which may be hæmorrhagic, is common. In severe cases there may be black vomit.

The mortality-rate in the Andamans is about 18 per cent.

The urine is highly coloured, nearly always containing albumin and bile, and sometimes casts and red blood-corpuscles. The amount passed is reduced, and the contained albumin may be considerable, and usually persists for seven to ten days, after which a trace only may be found. The blood-urea is usually raised before the tenth day of the disease, and a secondary rise occurs also during the secondary fever. The leptospira may be demonstrated in the urine from the tenth day onwards, and may persist as long as 100 days, and rarely can be seen in the blood from the twelfth day onwards. Prostration may be extreme. Constipation is the rule; the fæces are pale in colour. The pulse is slow in the later stages, and the blood-pressure low. A polymorphonuclear leucocytosis is present with an Arneth "shift to the left"; later there is said to be an increase in the lymphocytes.

After three or four days, in mild cases, the fever subsides by lysis. Slight or even severe febrile relapses are often seen at the beginning of the third week.

The liver may be enlarged, but splenomegaly is quite exceptional: the gall-bladder is distended, and tender on palpation; the lymphatic glands, more especially the inguinal and axillary, are frequently palpable and tender. Usually severe pain is noted in the primary attack as well as in the recrudescent period.

Typhoidal, uræmic, and meningeal forms—all of great gravity—have been described. In the meningeal, the cerebro-spinal fluid is under pressure, and contains an excess of albumin and leptospiræ in large numbers. Murgatroyd has described a peculiarly chronic meningeal form in which the leptospiræ were recovered from the cerebro-spinal fluid six months, and from the urine eight months, after the onset of the illness. The patient recovered subsequent to intrathecal injection of antileptospiral serum. Mollaret and Erber have found that the simple forms of leptospiral meningitis are comparatively common in France. Fatal cases are usually associated with paraplegia.

Epistaxis, hæmaturia, melæna, hæmoptysis, deafness and pharyngitis have been noted as complications, and also inflammatory ocular changes, such as iritis and irido-cyclitis. A secondary fever, or recrudescence with "rigors," may occur about the seventeenth day

without the recurrence of jaundice. The sequelæ are anæmia and debility. Alopecia usually occurs in convalescence.

Martin and Pettit recognize the following clinical forms of the disease :

1. Cases with grave icterus.
2. Cases of the true infectious-jaundice type, with febrile recrudescence.
    (*a*) Benign catarrhal.
    (*b*) Prolonged febrile.
    (*c*) Meningeal.
    (*d*) With nervous syndrome.
    (*e*) Pulmonary.

Diagnosis.—The urine from the fifth to the eighth day is said to give an intense green reaction when one or two drops of acetic acid are added. Early in the disease, if possible before the third day, the blood should be examined under the dark illumination for leptospiræ, and in doubtful cases should be inoculated into guinea-pigs for confirmation. For this purpose 6 c.c. should be injected directly into the peritoneal cavity ; citrated blood acts equally well if not kept longer than twenty-four hours. The diagnosis may also be made, probably with more certainty from the twelfth day of the disease onwards, by the injection of the same quantity of catheterized urine. According to Fletcher, the diagnosis is most simply and readily made by direct inoculation of the blood into blood-agar, and subsequent incubation. Blanchard and Lefrou (1922) increased the chances of finding the parasite by triple centrifugation of the blood. According to Schüffner one centrifugation of 10 minutes' duration at 1,500 revolutions is useful in demonstrating leptospiræ when the plasma is separated from the precipitated red blood-corpuscles and examined in a thick layer. The disease has to be differentiated from yellow fever, catarrhal jaundice, syphilitic disease of the liver, the icterus of relapsing fever and of malaria. The fever must be distinguished from that of relapsing and of yellow fever, and the leptospira from *Spirochæta recurrentis*. On clinical grounds the diagnosis should not be missed, when jaundice is associated with nephritis and nitrogen retention and is followed by headache, muscular pains and scattered hæmorrhages.

In fevers such as typhus and cerebro-spinal fever, and in several others in which relapse may occur, including plague, rat-bite fever, and paratyphoid, especially paratyphoid-B, jaundice may occur as a complication.

An agglutination test for this disease has been devised by Martin, Pettit, and Vaudremer, using a culture of the leptospiræ grown on solid media ; it occurs in a titre of 1 in 500, 1 in 1000, and even as high as 1 in 30,000 (Davidson *et al.*). The specific agglutinins appear in the serum as early as the sixth, more generally about the tenth day of the illness, and persist for as long as twenty-two months.

Postmus (1933) has found that the properties of the serum persist for eight years or longer. In carrying out the serological test Schüffner uses living cultures of leptospiræ and also cultures killed and preserved in formalin. These formalinized leptospiræ resist the action of lysins in the immune sera, but agglutinate up to the highest dilution compatible with the strength of the serum. With living leptospiræ agglutination appears only in the lower dilutions but in higher ones lysis sets in, rendering agglutination impossible. There is one disadvantage that the formalin mixture after some weeks is rendered useless by the leptospiræ becoming matted together into felt-like clots. The agglutination-absorption test has been used by Schüffner and others as a means of differentiating strains of pathogenic leptospiræ ; thus he has been able to separate *L. canicola* of the dog.

Brown and Davis have shown that the "adhesion phenomenon" is applicable to the diagnosis of Weil's disease as well as of trypanosomiasis. The reaction possesses distinct advantages over agglutination owing to the ease and certainty with which it can be practised. The test consists in allowing the immune serum to interact with the specific leptospira in the presence of a suitable indicator such as bacilli or blood-platelets. Not only can the disease be diagnosed by this method, but it also furnishes a means of differentiating leptospiræ. It was shown that *L. icteroides* of Noguchi and *L. icterohæmorrhagiæ* are identical and *L. hebdomadis* quite distinct.

Smith and Tulloch use a macroscopic agglutination test. The antigen is prepared from actively growing young cultures of leptospira. The volume of culture added is equal to six times the volume of each dilution of the serum tested. The mixture of serum and culture is incubated for three hours at 37° C., followed by thirty minutes at 55° C. The results are read by oblique illumination and a hand lens. The ease with which this method can be carried out renders it one of practical importance.

Gaentgens has elaborated a complement-fixation test. The antigen is a culture of leptospira, centrifuged, and the sediment suspended in saline containing 0·3-per-cent. carbolic acid.

The centrifuged deposit of urine rich in these parasites may be utilized in place of a culture, and the diagnosis of infectious jaundice has by these means been placed upon a scientific, if not on a practical basis. The leptospiræ can usually be demonstrated in large numbers in the centrifuged urine, and may be present up to the sixty-sixth day, though they generally disappear on the fortieth. Davidson has pointed out that they are somewhat inconstant and disappear altogether in acid urine. If negative at first, it is recommended that this test should be repeated every second day up to the end of the third week.

An anti-spirochætic serum specific for the *Leptospira icterohæmorrhagiæ* has now been prepared from rabbits, and by this means the identification of the organism has been made possible.

From the fifteenth day onwards what is known as the immunity reaction may be employed ; for this purpose 1 c.c. of the patient's serum is left in contact, for fifteen minutes, with several times the lethal dose of the leptospira, and injected into a guinea-pig, which will not develop symptoms of the disease, while the control animals will die. A high blood-urea of 200–300 mgm. is usually found, but is not necessarily serious.

The differentiation of Weil's disease from yellow fever on clinical grounds may be difficult, but Faget's sign is not present in Weil's disease (*see* p. 366).

Treatment

1. General conduct of case.—The systematic treatment consists in keeping the patient at rest and flushing out the bowel by means of repeated small doses of calomel, and by intravenous injection of normal saline containing 5–10 per cent. of glucose. Should the nephritic symptoms become severe, intravenous injections of saline or of Ringer's solution, ½ to 1 litre, become necessary. The diet must be liquid and, if vomiting is persistent, should be given as nutrient rectal enemata. For the pruritus accompanying the icterus, spirit of camphor or mentholated vaseline is recommended.

2. Antiserum treatment.—The scientific treatment consists in the administration as soon as possible of a polyvalent antiserum which is prepared from horses injected with cultures of *L. icterohæmorrhagiæ*. Such an efficient serum is now prepared by Burroughs Wellcome. This is given intravenously at intervals of several hours for at least four days in succession; 20 c.c. at least should be given at each injection. For a man of 70 Kg. weight, the dosage is 60 c.c. daily for three to five days. Usually, following this treatment, the temperature begins to fall, but in advanced cases in which jaundice and uræmic symptoms have supervened, the method is of little value. Failing the provision of commercial anti-leptospiral serum, the serum of patients convalescent from this disease has been injected in daily doses of 30–40 c.c. intramuscularly. In order to give the best results this immune serum should have an agglutination and lysis titre of 1 : 20,000, and this is reached 30–50 days from the commencement of the attack. It deteriorates when stored and should not be used after six months.

3. Other measures.—*Hexamine* has been recommended and *Sodium tartrobismuthate* has given good results when injected subcutaneously. Uhlenhuth and Seiffert have recommended injections of a compound known as Bismuth-Yatren A and B.

Prophylaxis.—Prophylaxis manifestly consists in sterilizing the fæcal and urinary discharges of the patients, and in waging war against the rat, the natural host of the parasite, and carefully guarding against its access to food. Swimming, especially using the "crawl stroke," in pools or rivers known to be the source of the disease should be avoided. Sewer workers must protect themselves against abrasions. Noguchi prepared a vaccine of killed cultures of leptospira which he used for prophylactic inoculation in Japan.

SEVEN-DAY FEVER

Synonyms.—Nanukayami; Shueki; Sakusku Fever (Japanese); Autumn Fever.

Definition.—A short fever, due to *Leptospira hebdomadis*, occurring epidemically during the summer months, especially in Japan (Fukuoka), and characterized by sudden invasion, severe headache, pains in the back and limbs, and pyrexia of a peculiar saddle-back, or occasionally of a continued type, lasting from six to seven days and associated with a pulse which is relatively slow in relation to temperature.

History.—Possibly this is one of several fevers included under the term "simple continued fever." Its differential diagnosis from dengue was rendered clear by the discovery in 1918 of the *L. hebdomadis* by Ido, Ito, and Wani.

Geographical distribution.—The home of the disease is Japan and it is found in China (Shan-si), and possibly occurs also in India and the Dutch East Indies. A disease of dogs in the Malay States has been proved by Fletcher to be produced by a leptospira of the *L. hebdomadis* type (possibly identical with *L. canicola* of Schüffner, *see* p. 230).

Ætiology.—*L. hebdomadis* resembles *L. icterohæmorrhagiæ* closely, but can be distinguished by serological reactions. The organism is said by Noguchi to be slightly longer, the elementary spirals almost geometrically equidistant. It is present, though in small numbers, in the blood-stream during the pyrexial period, and may be demonstrated by Leishman's stain or by the dark-ground illumination, and is readily cultivated by Noguchi's method. The chief channel of elimination is by way of the kidneys and urine.

The short-eared field-vole (*Microtus montebelloi*) would appear to be the normal host of the leptospira in Japan, and the organism can be detected in the kidneys and urine of 3·3 per cent. of these animals, which can convey the disease by means of their bite. The endemic area of prevalence of seven-day fever corresponds with the distribution of this vole in Japan.

The *Microtus*, sometimes termed a field-mouse, in reality a stump-tailed field-vole, is common in country districts in Japan. It burrows in the ground and feeds on roots and grain in much the same manner as other small rodents.

The blood of convalescents from seven-day fever contains specific immune and spirochæticidal bodies, and when it is injected, together with a culture of the organism, into the peritoneal cavity of a guinea-pig, a positive Pfeiffer reaction is obtained. Young guinea-pigs are susceptible to inoculation with the blood of patients, and with cultures of the leptospira; they may also be infected *via* the skin or *per os*.

Symptoms.—The symptoms resemble those of infectious jaundice, and the blood shows a slight leucocytosis. The disease appears to be transmitted by the bite of infected field-mice, so that the patients are generally workers in the fields and forests.

After a short invasion-period the fever comes on briskly, and is accompanied by depression, muscular pains, especially in the calves, conjunctivitis, digestive symptoms, and enlargement of the lymphatic glands. Apparently seven-day fever is a mild disease; it has no mortality, and no distinctive pathological anatomy. The organism can be demonstrated in considerable numbers in the urine of patients after the eighth day, and may persist to the thirty-ninth day. Albuminuria is noted in the early stages.

Differential diagnosis.—The disease is to be distinguished from relapsing fever, infectious jaundice, rat-bite fever, and especially from dengue. There is considerable difficulty in the differentiation from the last, for many writers have confused the two diseases, and some consider them to be identical, but in view of recent work there can be little ground for adopting this view.

The bone-pains and the morbilliform eruption in dengue suffice to distinguish it from seven-day fever.

Treatment.—The disease being generally slight no specific treatment has been evolved. The fever must be treated on general lines.

NOTE.—In Sumatra various observers have isolated leptospiræ from illnesses of different degrees of severity, including fevers of from one to five days' duration with no jaundice; more severe cases with jaundice; and finally, hæmoglobinuric cases resembling blackwater fever (*see* p. 87). The organism isolated from mild cases is morphologically identical with *L. icterohæmorrhagiæ* and may produce severe symptoms on inoculation into guinea-pigs. Vervoort (1923) has proposed the name of *L. pyrogenes* for organisms isolated from these fevers of short duration.

Fletcher in the Malay States has also isolated leptospiræ from a variety of febrile cases, some resembling dengue, and he has classified the organisms serologically into a number of groups. Owing to the instability of serological reactions, and the fact that primarily non-pathogenic water leptospiræ may be rendered pathogenic so as to produce symptoms of Weil's disease in animals, Baermann and Zuelzer have reached the conclusion that all so-called pathogenic leptospiræ are identical with free-living forms in water. *L. icterohæmorrhagiæ* and *L. hebdomadis* may therefore be identical.

CHAPTER VII

RAT-BITE FEVER

Synonyms.—Sodoku—*so* (rat), *doku* (poison) ; Sokosha (Japanese) : Cat-bite Disease.

Definitions.—An acute febrile disease caused by *Spirillum minus* (*morsus-muris*), inoculated into man by the bite of an infected rat, causing a local disturbance at the site of infection, followed by a general fever, with a tendency to relapse and, in some cases, a cutaneous eruption.

History.—This disease has long been known to Japanese physicians. Since its recognition, cases have been reported from India and other countries. In 1915 Futaki, Takaki, Taniguchi, and Osumi demonstrated spirilla in the lymphatic glands from the tenth to the thirteenth day of the illness ; later they found similar, though shorter and stouter, organisms in the blood-stream ; the latter are now recognized as being the young forms of the parasite. This work has since been confirmed by Kaneko and Okuda in 1917, and by R. Row in Bombay. As a result of investigations, A. Robertson has shown the organism to be a spirillum, and its correct nomenclature to be *Spirillum minus* Carter, 1887.

Geographical distribution.—Rat-bite fever appears to have a widespread distribution, but it is especially common in Japan. Cases have been reported in Great Britain by Horder, Low, Atkinson, and Joekes, and from the United States, Germany, Italy, Australia, and East Africa.

Ætiology.—*S. minus*[1] is a short, squat spirillum differing greatly from spirochætes, at any rate when in the human body. It measures 1·5–6 μ in length ; the pointed extremities are continued into one or more flagella ; including this, the total length may be 15 μ. (Fig. 35.) The curves are regular, and generally number three or four, or even six or more. It is difficult to demonstrate in the blood in the living state even by means of the ultramicroscope, but it may be seen in the exudate in the neighbourhood of the bite, and in the juice from the superficial lymphatic glands.

Movements.—In the living state the organism, under the microscope, moves rapidly like a vibrio, by means of lashing movements of the flagella ; the body itself is held rigid, and in this manner the movements can be readily distinguished from the vibratile motions

[1] Formerly known as *Spirochæta morsus-muris*.

of the true spirochætes. This fact, together with a certain amount of doubt regarding its method of multiplication, has led to some controversy as to its systematic position. The presence of the spirillum can be easily verified in suspicious cases by inoculation of white mice with any of the material in which it can be seen. Next to mice, white rats and guinea-pigs and monkeys (*Macaca rhesus*) are most susceptible. The spirillum can also persist in the blood of dogs without giving rise to any obvious symptoms. In mice, Ozeki has shown that the infected animals can be recognized within one or two months after infection by the loss of hair on the belly and chest and the nasal line, including the eyes and ears. Usually, however, experimental animals survive. The organisms appear in the blood-stream about seven days after inoculation, and persist for several months. The disease can be transmitted by the brown rat (*Rattus norvegicus*) and the black rat (*R. rattus* and *R. alexandrinus*), and by the bite of a ferret or of a cat.

Fig. 35.—*Spirillum minus* **of rat-bite fever in mouse.** 1,500.
(*Photomicro.: Dr. A. C. Coles.*)

The organism resembles, and is probably identical with, *S. laverani* and *S. muris*, which have been found in the blood of rats and mice in various parts of the world. Saisawa and Taise have shown that the spirilla can be found in large numbers in the peritoneal fluid of mice, and when these animals are treated with small quantities of neosalvarsan the organisms persist in the brain and in the spleen. Like the true spirochætes, they have the power of forming remarkable agglomerations, sometimes forming balls 40–50 μ in diameter. Under the dark-ground illumination, these clumps move like a rolling ball.

Jockes has succeeded in cultivating *S. muris*, which he found in 25 per cent. of the wild rats in London, by using an inspissated horse-serum slope, as employed for the diphtheria bacillus, over which is poured Vervoort's medium (1-per-cent. peptone to which are added 3 c.c. of normal phosphoric acid). Primary culture is obtained by inoculating the medium with blood from an infected guinea-pig and incubating at 37° C. Subcultures are easily maintained in 1-per-cent. glucose broth.

The immunity conferred on man and on animals during an attack of this fever is permanent, and protects, apparently, against all other organisms of the same type that have been procured from various sources.

Symptoms.—The *incubation period* varies from one to sixty days: the average being from five to ten days, during which time the wound heals. The cicatrix itself, and sometimes the surrounding tissues, become inflamed, with formation of blebs and even necrosis. The lymphatics draining the area are implicated, and the glands themselves become swollen and tender. The onset of the fever is characterized by rigors and malaise; the temperature gradually rises in three days to a maximum of 103–104° F., and, after a further period of three days, ends in crisis with profuse sweating.

After the primary attack a quiescent interval of five to ten days ensues, with subsidence of the local disturbance. One or more relapses (Chart 11) associated with the same symptoms, and in addition a characteristic purple papular exanthem or urticaria on the chest and arms, have been noted. The eruption is sometimes nodular.

In most cases the reflexes are increased; there may be pains in the muscles and joints, and hyperæsthesia and œdema of various parts of the body. The death-rate is about 10 per cent. The end is ushered in by delirium, often lapsing into coma.

As in relapsing fever, the organism can be demonstrated

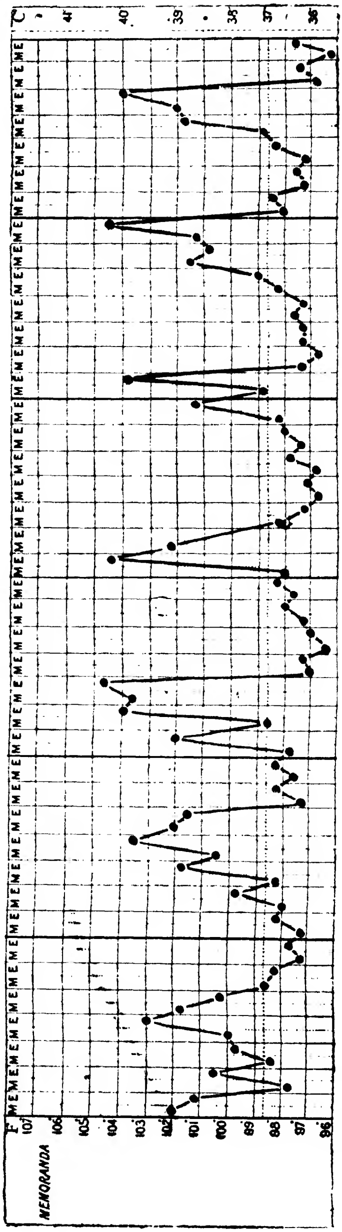


Chart 11.—Rat-bite fever, showing periodic relapses. *(By permission of London School of Hyg. and Trop. Med.)*

in the blood during the fever only, disappearing during the apyretic intervals. The serum agglutinates the spirillum in low dilutions. There is an eosinophilia during the paroxysm and a moderate leucocytosis of about 15,000. It is said that the serum in this disease gives a weak positive Wassermann reaction.

Pathology.—In the fatal cases the lymph-glands are swollen, the spleen is enlarged, the liver hyperæmic, and the lungs may show hæmorrhages. The cornea is often involved. The spirilla have been demonstrated in the liver, spleen, kidneys, suprarenal glands, eyes, and testicles.

Diagnosis.—In many cases the diagnosis of rat-bite fever can be fully established from the history, the infiltration at the seat of the bite, the typical temperature curve, the rash, and the effects of the administration of salvarsan. This diagnosis can be confirmed either by dark-ground illumination, when spirilla may be seen in the exudate obtained from the site of the bite, or in the serous fluid from the papule, or by Giemsa-stained smears. It is seldom possible to demonstrate spirilla in a thick blood-film. If a number of relapses have occurred, probably the best examination to make is one for the presence of lytic antibodies.

Differential diagnosis.—This has manifestly to be made from the different forms of relapsing fever and trench fever, with which the temperature chart has much in common. In tropical countries the possibility of a coexistent malarial infection has to be taken into account. The puffiness of the face accompanying the urticarial eruption may simulate Bright's disease.

The reaction occurring around the site of the scar is apt to be confused with erysipelas.

Treatment.—Salvarsan and its derivatives act as a specific. As a rule, one injection of novarsenobillon (0·4 to 0·6 grm.) is sufficient to effect a cure.

Neoarsphenamine is the name officially adopted in place of novarsenobillon, neosalvarsan, etc.

Occasionally the intravenous injection has to be repeated as a prophylactic measure. Schoekaert has shown that antimony preparations, especially *stibosan,* given in therapeutic doses, are effective in rat-bite fever ; on the other hand, tartar emetic and antimosan have no effect on the spirillum. A cat- or rat-bite should always be cauterized.

As in syphilis (*Spirochæta pallida*), so in rat-bite fever the bismuth compounds appear to have a definite curative value. Montel and Truong-Van-Que have advocated *Bivatol,* which they have given intramuscularly at intervals of three and five days. Two cases were completely cured after four intramuscular injections.

Prophylaxis.—Quite obviously the prophylaxis of this disease, as in plague, rests upon an efficient method of rat destruction. In Manila, for instance, it has been found that the distribution of rat-bite fever and plague in that city are co-extensive and that therefore measures taken against one are in fact effective against the other.

Subsection C.—FEVERS CAUSED BY BARTONELLA AND RICKETTSIA BODIES

CHAPTER IX

BARTONELLOSIS

(OROYA FEVER AND VERRUGA PERUANA)

MEDICAL opinion in Peru has always regarded Oroya fever and verruga peruana as clinical manifestations of the same disease. For a time this view appeared to be negatived as the result of the work of the Harvard Commission in 1915, but the important work of Noguchi on the cultivation of the virus of Oroya fever and the subsequent production of verruga-like lesions on inoculation into monkeys has certainly settled the question of the unity of these apparently distinct diseases. Mayer and Kikuth in Germany have fully confirmed the work of Noguchi in every respect, so that these two apparently dissimilar diseases must now be regarded as the generalized and localized manifestations of the same infection.

OROYA FEVER STAGE (GENERALIZED BARTONELLOSIS)

Synonym.—Carrion's disease.

Definition.—An acute specific fever, endemic in certain valleys of the Andes, and characterized by a rapidly developing anæmia of the pernicious type, irregular pyrexia, and great tenderness over the blood-forming tissues. The organism is *Bartonella bacilliformis.*

History.—The first attempt to settle the ætiology of this disease was made by the self-sacrifice of Carrion, a medical student who, in 1885, fatally inoculated himself with the blood from a verruga nodule in Lima. From this experiment the Peruvian physicians concluded that the verruga and Oroya fever were different stages of the same disease.

It is thought that Oroya fever was the disease which proved so fatal to Pizarro's army in the sixteenth century. In order to reconcile the observations on the development of the eruptive stage without a severe febrile preliminary stage lasting three to four weeks, it has always been considered that the first stage might be exceedingly mild.

Geographical distribution.—Between the 9th and the 16th parallels of South latitude, and at an elevation of from 3,000 to 10,000

feet, in certain narrow valleys of the western slopes of the Andes, this peculiar fever is endemic. It is therefore found in Peru, Ecuador, Bolivia, and Chile. Its topical as well as its geographical range is singularly limited; it is confined to certain hot, narrow valleys or ravines, the inhabitants of neighbouring places being exempt.

It is said that the disease may be acquired when merely journeying through the endemic districts, more especially if the traveller passes the night there.

Ætiology.—Although out-of-door workers are the most subject, all ages classes, and both sexes, including infants, are liable to attack. During the fever certain rod-like bodies are to be found in a large proportion of the red

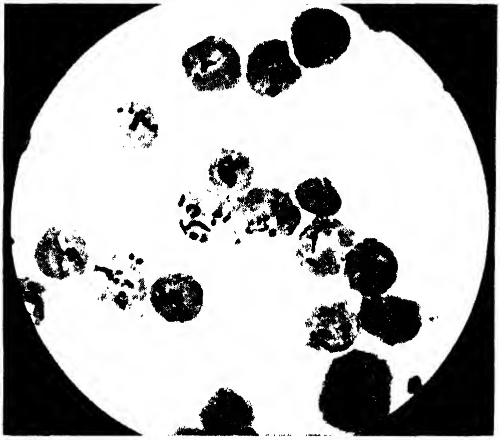


Fig. 36.—Blood smears with numerous *Bartonella bacilliformis* **(human Oroya fever).** (*Kikuth.*)

blood-corpuscles (Fig. 36), and in endothelial cells of the lymphatic glands. These were first noted by Barton in 1909, and were considered by him to be protozoal in character; these findings were subsequently confirmed by Strong and other members of the Harvard Commission, and the bodies were termed by them *Bartonella bacilliformis*. They somewhat resemble stages of a piroplasm (*Theileria parva*) during its cycle in the lymphatic glands, and similar bodies are found in the blood of normal mice and certain rodents (*Bartonella muris*), which, as Mayer, Borchardt and Kikuth have shown, exist as a latent infection, but which may produce an acute and fatal anæmia, resembling Oroya fever, subsequent to removal of the spleen. The causal organism of dog-anæmia following splenectomy is *Bartonella canis*. The clinical course of this infection is connected with an endothelial reaction, and and organism is transmitted by rat-lice (*Hœmatopinus*). Chemotherapeutic experiments have led to the discovery of an effective arsenic-antimony compound with an index of 1 : 3500, which is a figure of efficiency never

heretofore reached in chemotherapy (Kikuth). On account of their peculiar behaviour, the *Grahamella*, first described by Graham-Smith in the blood of moles, should be kept apart from *Bartonella* and regarded as a separate genus.

Two forms of *B. bacilliformis* are recognized—one is a rod-shaped, slightly curved bacillary organism 2 μ long by 0·5 μ broad, staining with Romanowsky an intense blue, often in branching forms and in chains, but never crossed; the other is a rounded body about 1 μ or less in diameter, usually oval or pear-shaped, and containing chromatin granules. Both are difficult to distinguish in fresh blood, and show feeble independent movement.

Noguchi regarded *Bartonella* as a bacillus and succeeded in cultivating it on solid media from specimens of citrated blood sent in "cold storage" from Lima to New York. The organism grows best at low temperature on blood-agar media. He was so successful in culturing the organisms that he recommended it in diagnosis as preferable to examining blood smears.

Battistini's method of culture is simple. A small drop of blood from the finger of the patient is withdrawn into serum-agar. The end is sealed in the flame and the whole placed in the incubator at 28° C. Colonies are visible in 5–6 days. The cultivated bodies are 0·6–1·6 μ in length. It is an obligatory aërobe and Gram negative, but stains well with Giemsa. Intravenous injections of cultures into *Rhesus* monkeys produced irregular fever and extreme anæmia; in the blood-cells the *Bartonella* organisms could be demonstrated. Intradermal injection into the supraorbital tissues gave rise to nodules resembling verruga. In excised nodules *Bartonella* survives for at least fifty-six days at 40° C. Noguchi succeeded in conveying the infection to monkeys by the bites of ticks (*Dermacentor andersoni*), but Townsend in 1913 conjectured that the insect vector was a sandfly (*Phlebotomus verrucarum*). Further evidence incriminating *P. noguchii* and *P. verrucarum* was obtained by Noguchi, Shannon, Tilden, and Tyler in 1929, and this was confirmed in 1937 by Pinkerton and his colleagues. Insects were collected in a verruga district of Peru and sent in sealed glass tubes to New York. They were then ground up in saline and the emulsion injected intradermally into monkeys. The only insects which showed any evidence of containing Bartonella were Phlebotomi.

Mayer and Kikuth were able to confirm Noguchi's studies in a case of verruga in Hamburg. An emulsion of an excised papule injected into monkeys produced typical lesions and Bartonella were observed in the blood of one of the infected animals.

The results of the Harvard expedition to Peru in 1937 were mainly confirmatory. Pinkerton, Wenman and Hertig confirmed the findings of Bartonella in blood culture. They recognized three types of Carrion's disease in man,

(1) the anæmic forms;
(2) the asymptomatic; and
(3) the cutaneous, which was reproduced by inoculation of (*a*) infected lymph-nodules, (*b*) human verruga tissue, (*c*) cultures of Bartonella from the blood of human verruga cases.

The disease is most prevalent from January to April, when the streams are in flood, the air hot, still, and moist, malaria epidemic, and insect life abundant.

Pathology.—A remarkable feature of this disease is the rapidity and extreme degree of blood destruction. In bad cases the blood-count may drop in three or four days to 500,000 per c.mm., the picture being that of a pernicious anæmia. There is a marked polymorpho-nuclear leucocytosis with disappearance of eosinophiles. The red cells are of the megalocytic type.

In addition to the anæmia, marked changes are present in the liver, spleen, and bone-marrow. In the liver, areas of degeneration and central necrosis are found around the hepatic veins. In the centre of the necrotic areas a yellow pigment resembling hæmosiderin is present in abundance. The spleen is invariably enlarged, and also contains necrotic areas with pigment in the pulp, but the Malpighian bodies themselves are not affected. The lymphatic glands contain large macrophage endothelial cells studded with rod-shaped bodies. The lesions in the viscera are considered by Strong to be due to toxins liberated by the parasite. The bone-marrow shows proliferation, necrosis, and marked phagocytosis of the large endothelial cells. Noguchi observed the same lesions in monkeys succumbing to Bartonella infection as have been recognized in man—in the spleen, endothelial cell hyperplasia and also in the lymphatic glands: in the bone-marrow an increase of macrophagocytes, and in some instances, normoblasts.

Symptoms.—The *incubation period* of Oroya fever is about three weeks. Its *onset* is insidious and is marked by malaise, soon followed by a rapidly developing pernicious anæmia and an irregular remittent pyrexia, associated with very severe pains in the head, joints, and long bones. The bone pains are probably connected with the disturbances in the hæmopoietic system. Very often the initial fever is like that of a malaria infection, and may be the outcome of a double infection in a malarial subject. The most severe types resemble a fulminating typhus and are known as the "severe fever of Carrion." The liver and spleen are enlarged and tender. The anæmia develops with great rapidity. The death-rate varies from 10 to 40 per cent. of those attacked, the end coming within two or three weeks of the onset of the disease. A terminal delirium is often noted. In those cases in which verruga ensues, the fever may last three to four months.

Treatment.—Kikuth has produced a most remarkable arseno-antimony compound, *Sdt.* 386 *B*, which has a selective action for *Bartonella*. The therapeutic index is very high and the margin between the *dosis tolerata* and *toxica* is a wide one. Manrique has reported the results in twelve severe cases with intravenous doses of 0·1–0·3 grm. repeated two to three times, and he succeeded in banishing *Bartonella* from the blood-stream and bringing about a rise in the blood-count. A total of up to 5–7 grm. of this substance was injected without any systemic disturbance being noted.

VERRUGA PERUANA STAGE (LOCALIZED BARTONELLOSIS), OR ERUPTIVE STAGE

Definition.—A remarkable granulomatous eruption confined to certain parts of Peru and neighbouring countries. It is associated with hæmorrhages, fever, and joint pains. The disease was known to Pizarro, and is described in Prescott's "Conquest of Peru."

Ætiology.—Superficially, the lesions of verruga resemble those of yaws.

Rocha Lima, Mayer, and Werner described chlamydozoa-like cell inclusions in the verruga nodules and considered them to be the cause of the disease. As already related, Noguchi has demonstrated Bartonella bodies in experimentally-produced lesions in monkeys. This work has been confirmed by Mackehenie, Weiss, Mayer and Kikuth, who have produced nodules in monkeys with human material and demonstrated Bartonella bodies within angioblasts or endothelial cells. Verruga is therefore but a local connective-tissue infection with *Bartonella bacilliformis.*

Strong's experiments upon monkeys showed that by graduated inoculation of verruga material he was able to induce an artificial immunity. Verruga can be conveyed by inoculation to rabbits and dogs, and according to Townsend occurs as a natural infection of native Indian dogs.

Pathology.—Primarily the pathological changes consist in a proliferation of the endothelium of the lymphatic channels, which become obstructed by plasma-cells and fibroblasts, but the structure is much more vascular than that of yaws, which it otherwise resembles. The capillary blood-vessels become dilated, so that the granulomatous tumours are vascular, almost cavernous, and prone to bleed profusely. A feature of the pathological histology is the formation around the blood-vessels of nodules of angioblasts characteristic of the disease. Bartonella bodies may be found in the blood-corpuscles after prolonged search (Mayer), but in monkeys, if the spleen be removed, they multiply exceedingly and produce Oroya fever.

Symptoms.—The period of incubation subsequent to Oroya fever is thirty to forty days, but in those cases in which the initial fever is absent it is at least sixty days. The initial stages are characterized by peculiar rheumatic-like pains, together with fever, the pains being apparently the same in character as those of yaws, only more severe. As in yaws, the constitutional symptoms subside on the appearance of the skin lesion. The eruption, like that of yaws (*see* p. 618), may be sparse or abundant, discrete or confluent. As in yaws, individual granulomata may fail to erupt; others may subside rapidly; yet others may continue to increase, and then, after remaining stationary for a time, gradually wither, shrink, and drop off without leaving a scar. If there be difference in clinical features between verruga and yaws, apparently it is more a difference of degree than of kind.

The eruption is generally described as being of two types, miliary and nodular—the former not exceeding the size of a small pea; the latter, the rarer form of the two, less numerous, but consisting of much larger nodular masses. The miliary eruption, as a rule, is found most abundantly on the face and extensor aspect of the extremities, less commonly on the trunk (Fig. 37).

A pink macule first appears, which later darkens in colour and becomes nodular. These nodules may be flat or somewhat pedunculated. The verruga artificially produced in monkeys by injection of Bartonella bodies is bright cherry-pink in colour.

We find no mention made of the occurrence in yaws of fungating granulomata in any situation but the skin. In verruga it would seem that these vascular lesions may develop on mucous surfaces—in the mouth, œsophagus, stomach, intestine, bladder, uterus, and vagina. Hence the dysphagia—a common symptom—and the occasional occurrence of hæmatemesis, melæna, hæmaturia, and bleeding from the vagina. Relapses both of the fever and of the eruption may occur.

Fig. 37.—Verruga peruana. (*After Odriozola.*)

In inoculated monkeys swelling of the lymph-glands is an early and constant symptom.

The tendency to spontaneous hæmorrhage is attributed to the diminished atmospheric pressure at high altitudes, for it is said that when patients descend to the lower valleys, or to the sea-level, the proneness to bleeding ceases.

The nodular eruption is more chronic than the miliary; individual lesions may grow to the size of a pigeon's egg; they may become strangulated, and a source of danger from hæmorrhage. This type of eruption does not invade the mucous membranes, and is usually confined to the regions of the knees or elbows. It appears in crops, and the duration of the disease extends over two or three months.

In contrast to Oroya fever, the mortality from verruga is practically nil.

Diagnosis.—The appearances of verruga are so characteristic that it is hardly likely to be mistaken for any other disease. Conceivably it may closely resemble the frambœsiform eruption of secondary yaws; it may also be simulated by multiple warts, molluscum contagiosum, multiple fatty tumours (Dercum's disease), and, according to Strong, it is closely allied to, if not identical with, Bassewitz's angio-fibroma cutis conscriptum contagiosum. Individual

tumours may resemble a fibro-sarcoma or an angioma. The Oroya and verruga stage frequently coexist.

Treatment.—Very little is known about the treatment of this condition. Small doses of salvarsan, 0·2 grm. intravenously, have been tried with benefit, and intravenous injections of Kikuth's *Sdt.* 386*B* are recommended. When individual tumours begin to ulcerate or become gangrenous they should be excised. Dangerous bleeding may occur, and styptics or compresses may be required to stay the excessive loss of blood.

CHAPTER X

THE TYPHUS GROUP OF FEVERS

Preliminary statement.—Although it was formerly confused with typhoid fever, typhus has been recognized since the middle of the nineteenth century as a disease having distinctive features. Typhus fever has an almost cosmopolitan distribution ; but it has now come to be recognized that, as in the almost comparable case of the relapsing fevers, a number of local forms, or varieties, can be distinguished. The existence of these special forms is probably due to the influence of local conditions in some way connected with the various arthropod intermediary hosts which convey the virus from one person to another.

The classical type of the disease, which is distributed in the Palæarctic and Nearctic areas, will be referred to as " true typhus," and the local varieties by their descriptive pseudonyms, such as " Brill's Disease," " Fièvre boutonneuse," " Rocky Mountain Spotted Fever," etc. It has been decided to adopt Megaw's table of classification based upon the nature of the insect vector, and although this forms a convenient basis for future work, it must be taken as provisional at the present time.

TYPHUS FEVERS (MEGAW'S CLASSIFICATION)

Typhus fevers

Epidemic " Louse " typhus (True typhus)	Non-epidemic typhus		
	Flea typhus (Brill's disease)	Tick typhus — Rocky Mountain spotted fever, etc.	Mite typhus

The further subdivision of typhus fevers has been made possible by the *Weil-Felix reaction.* This has been established as a test for typhus since 1916, as a specific serological diagnosis for true typhus in Europe, and therefore it could be expected to be positive for the louse-borne typhus in other parts of the world. It has been established also that this reaction occurs in those aberrant typhus-like fevers which differ from the classical type and are certainly not transmitted by the louse.

In the present state of our knowledge it suffices to say, as a pre-

liminary statement, that diseases of the typhus-group are probably caused by certain minute organisms, known as *Rickettsia*.

Rickettsia are gram-negative bacteria-like bodies, usually less than half a micron in diameter, found intracellularly in the alimentary canal of certain insects and other arthopods. There are five named species. The organism, originally termed *Dermatocentroxenus rickettsii* by Wolbach, which was first described by Ricketts, is now known as *Rickettsia rickettsii*, and is the cause of Rocky Mountain fever. Sellards, in 1923, claimed to have cultivated the organism of Japanese River fever (tsutsugamushi) in Japan, and has named it *Rickettsia orientalis*. In 1916 Topfer described a similar organism in lice taken from patients suffering from Wolhynian fever (trench fever), and this appears to be identical with *Rickettsia pediculi* described by Da Rocha Lima in apparently healthy lice, whilst the organism of trench fever has been alternatively known as *R. quintana* and *R. wolhynica*. The rickettsia of true typhus is known as *Rickettsia prowazeki* after its discoverer, von Prowazek, who, like Bacot at a later date, succumbed to an accidental infection. Rickettsia are found in the alimentary tract of blood-sucking and in non-blood-sucking insects; but, probably, they were primarily inhabitants of the cells lining the canal. In their morphology rickettsia appear as small bacilli or cocci, their arrangement being very variable. Diploid forms are common and also coccoid forms grouped in dense masses. With the possible exception of *R. orientalis*, they stain well by Giemsa's method. None of the pathogenic species has been actually cultivated from living cells, though practically pure strains of *R. prowazeki* may be obtained by a method of intrarectal injection of body-lice with infective material, and Arkwright and Bacot in 1923 found that *R. prowazeki* remained virulent for 11 days in louse excreta which had been kept dry at room temperature.

Pinkerton has pointed out from the pathological point of view that the two main forms of typhus—the louse-borne and the tick-borne—may be differentiated by their cellular reactions. *True typhus*, carried by lice and fleas (Insecta), is characterized by invasion of the endothelium and mesothelium only by Rickettsia, producing distension of the cytoplasm of the host cells without affecting the nuclei, whilst in guinea-pigs it causes proliferative endangitis without thrombo-necrosis.

In typhus-infected lice and fleas the Rickettsia organisms are intracytoplasmic; they infect the lining of the gut and are not hereditarily transmitted. The *spotted-fever group*, which are transmitted by ticks (Arachnoidea), are characterized by histo-pathological lesions—thrombo-necrosis of arterioles and venules. The infecting organisms (Rickettsia) invade smooth muscle cells, endothelium, mesothelium and macrophages.

In tissue culture massive invasion of cell nuclei takes place. In the infected ticks the organisms are intranuclear as well as intracytoplasmic; they invade nearly all types of tissue and are transmitted hereditarily.

These types and strains of typhus virus are so closely allied that their conversion one into the other could be anticipated. This Mooser, Varela, and Pilz (1933) appear to have done. They have devised a method by which these epidemic non-orchitic strains can be converted regularly into murine strains causing scrotal lesions in guinea-pigs.

This method consists of daily blood injections intraperitoneally into rats inoculated with the virus. The observation is based on the fact that *Rickettsia prowazeki* multiplies only within those cells which come into frequent

TYPHUS GROUP

Disease	Distribution	Reservoir	Vector	Virus
1. Louse-borne Epidemic Typhus.	World-wide.	Man.	Louse (*Pediculus humanus*).	*Rickettsia prowazeki*.
2. Flea-borne Endemic Typhus: Brill's Disease.	World-wide.	Rat.	Flea (*X. cheopis*).	*R. prowazeki*.
3. Fièvre nautique (Local form of Brill's Disease).	Toulon and Athens.	Dog.	Flea (*X. cheopis*).	*R. prowazeki*.
4. Tropical Typhus (Urban (shop) "W" form).	Malaya, Sumatra. W. Africa (?)	Tropical rats.	Flea (*X. cheopis*).	*R. prowazeki*.
5. Tick-borne Typhus (Rocky Mountain fever).	N. America, West & East.	Squirrel, woodchuck.	Tick (*D. andersoni*. *D. variabilis*).	*R. rickettsii*.
6. Tick-typhus (Fièvre boutonneuse.	Mediterranean region.	Dog.	Tick (*Rhipicephalus sanguineus*).	*R. conori*. *R. canis*. (?)
7. Tick-bite fever (African form).	S. Africa, Kenya.	Dog. Small veld rodents.	Tick (*R. appendiculatus*. *Boophilus decoloratus*. *Amblyomma hebræum* (?).	
8. Tick-bite fever (Indian form).	Kumaon Hills (India).	(?	Tick (*R. sanguineus* (?) *Hyalomma ægyptium*).	
9. Tick-typhus (S. American form).	Brazil.	Domestic & wild dog. Rabbit & agouti.	Tick (*Amblyomma cayennense*).	*R. braziliensis*
10. Mite-typhus: Japanese river fever (Tropical typhus, Scrub "K" form).	Japan, Sumatra, Malaya, Cochin-China.	Field mice. Tropical rats.	Mite (*Trombicula akamushi*, *T. deliensis*).	*Rickettsia orientalis*.

Felix considers that the viruses of the typhus diseases correspond to various types of *Proteus*.

X19 corresponds to epidemic and endemic typhus, XK for scrub typhus and for Japanese river fever. The South American form (*see* p. 263) differs from epidemic

OF FEVERS

Clinical Spmptoms. Fever, Rash	Neill-Mooser Reaction in Guinea-pigs	Typhus Nodules	Weil-Felix Reaction. *B. proteus* X	
			Type X19	Type XK
Present.	Only very occasionally.			
Present.	Constant.			
Present.				
Present.	Present.			
Present.	Constant + Gangrene.			+ + +
Present + Primary ulcer.	Present.			
Present + Primary ulcer.	Present.			
Present.				
Present.	Present.			
Present + Primary ulcer.	Present.			+ + +

and endemic typhus in containing agglutinins to both X19 and XK (group agglutinins).

Additional strains of proteus have been worked out and give anomalous results. X_2 is one of the original strains of proteus and XL a new variety isolated by Dr. Lima of São Paulo. " Q fever " has been omitted as complete information is lacking.

contact with fresh blood. It is concluded that no real difference exists between the virus of the historic old-world typhus and the murine new-world typhus. Both are considered to be of murine origin.

The experiment is as follows: a transfer guinea-pig received a daily rat-blood inoculation intraperitoneally for six days, and on the seventh day the animal showed fever and a typical scrotal swelling with numerous rickettsia in the tunica. After a few more transfers through rats this strain, which previously had caused no apparent infection in rats, killed them regularly between 4–8 days. On further transfers from guinea-pig to guinea-pig, the strain rapidly reverted to its nonorchitic original source. It is therefore considered that in the mammal, as well as in the insect, *Rickettsia prowazeki* is dependent for its intracellular development on the presence of fresh blood, which has come into contact with susceptible cells.

Cultivation.—The rickettsia have so far not been cultivated with certainty on artificial media, although Anigstein has produced certain appearances on growth which lead him to suppose that a close connection exists between these organisms and *Bacillus fusiformis* (*see* p. 270). Other methods of cultivation on tissue-culture have recently been introduced by Japanese workers. It has thus become possible to state in a general way that the disease known as typhus has two main manifestations—the first and better-known is *true typhus*—a louse-borne disease of great communicability from one person to another in times of overcrowding amongst an unclean population, and characterized by its tendency to the formation of epidemics; the second (*endemic typhus*), a disease primarily of rodents which is transmitted from rat to man by rat-fleas. This manifestation of typhus is, seemingly, not transmitted from man to man direct and is therefore characterized by its tendency to remain *endemic*.

I. EPIDEMIC OR TRUE TYPHUS FEVER

Synonyms.—Typhus Exanthematicus; Tabardillo (Mexico).

Definition.—An acute fever of abrupt onset, lasting about fourteen days, and, if not fatal, terminating about the fourteenth day by crisis. The pyrexia is of a remittent type. On or about the fifth day there appears a roseolar eruption tending to become petechial, and spreading from the abdomen over the trunk and extremities. The virus is conveyed by lice.

Louse-borne typhus has a world-wide distribution throughout Europe, Asia and America. It is found on the North-west Frontier of India, and in North Africa north of the Sahara, also on the Belgian Congo (Pergher and Casier), and in Cochin China (Lépine), as well as in Central and South China and Manchuria.

Geographical distribution.—The disease has been eradicated in peace times from most civilized European countries, but reappears in epidemic form in periods of stress and famine, as in the Great War. In certain subtropical countries, as in North Africa, it is widespread.

Ætiology.—True typhus is conveyed by lice (*Pediculus humanus*

var. *corporis* and *capitis*); the virus is filterable, and is infective for monkeys and guinea-pigs; it is present in the blood-plasma, especially in the blood-platelets, during the first five days of the disease (Bacot and Ségal). A developmental cycle probably takes place in the body-cavity of the louse, which is infective only from the fourth to the seventh day after a meal of typhus blood. Infection is conveyed through the fæces of the louse and is inoculated by scratching. Arkwright, Wolbach, Todd, and others described a minute organism, *Rickettsia prowazeki*, which occurs in the body of the louse, as the causal organism. Anigstein and Anzel (1930) have been able to culture the rickettsia from the blood on their special medium (*see* p. 270).

Wolbach and Schlesinger have found that the virus of typhus survives in tissue-plasma cultures for a length of time corresponding to the life of the endothelial cells multiplying in the cultures, and the micro-organism can be found in them in large numbers, coccoid, bacillary, and filamentous forms being noted. Brain-tissue cultures from typhus guinea-pigs have proved most successful. Guinea-pig's blood is used as the source of the plasma, and collected in paraffin-lined tubes, centrifuged, and chilled. The tissue for cultivation is obtained with aseptic precautions and kept immersed in Ringer's solution, the pieces of tissue for cultures being cut into blocks 0·5–1·0 c.mm. in size, transferred to a sterile cover-slip, and covered with sterile plasma. On transferring tissue cultures to fresh plasma, pieces of tissue are first washed in Ringer's solution, and the virus can be kept alive from four to six weeks.

In 1917 Neill described a distinctive reaction in guinea-pigs inoculated with typhus blood. In 70 per cent. a redness and swelling of the scrotum appeared (comparable with a similar reaction in Rocky Mountain fever). Typical lesions are found in the vessels of the scrotum, but mostly in the endothelial lining of the tunica vaginalis. In sections of this membrane swollen endothelial cells, packed with *Rickettsia* organisms, are to be seen. Recent observers now claim that the reaction is not usually positive with true typhus as it is in some of the other varieties. Usually only fever is produced without local scrotal reactions. However, the blood of the patient taken within the first three days of the disease, when inoculated into guinea-pigs, produces, after an interval of 8–10 days, a characteristic fever. Sometimes, however, it fails to do so; then the virus is concentrated in the brain, for an emulsion of this organ in a non-reacting guinea-pig produces typical fever when inoculated into a second animal, and the animals fail to react again when injected with typhus blood on a second occasion. Noury has shown that the virus can also be easily transmitted by an emulsion of the infected spinal cord.

Pathology.—The blood is dark-coloured, and does not clot; the liver and kidneys show cloudy swelling. There is generally a moderate enlargement of the spleen, with hyperplasia of the lymph-follicles; the substance is soft and diffluent. Bronchial catarrh is generally present, with hypostatic congestion of the lungs. There are no changes in the Peyer's patches; the mesenteric glands are not affected, typhus being thus differentiated from typhoid fever. The eruption is due to a localized necrosis of the walls of the smaller

blood-vessels, with local collections of lymphocytes and plasma-cells in the adventitia. These nodules, which are characteristic, are found in the brain and viscera, as well as in the skin. The essential lesions are due to a phagocytosis by the vascular endothelium, followed by necrosis of these cells.

Symptoms.—The *incubation period* varies between four and fourteen days, twelve being the average. The period of *onset* lasts about two days, during which time the patient may experience headache, nausea, giddiness, etc. Occasionally, in fulminating cases general convulsions occur, passing into delirium. On the third day the temperature rises suddenly to 103° or 104° F., the face becoming congested, the eyes suffused. (Chart 12.) There is a peculiar stuporose, drunken look, such as is not found in any other disease—except,

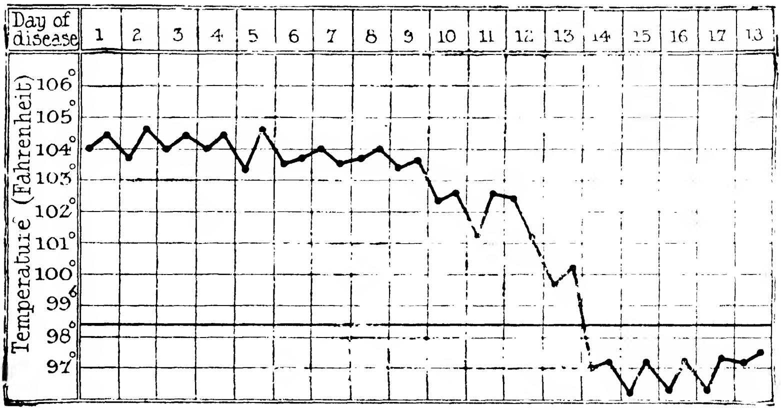


Chart 12.—**Typhus fever.** (*Orig.*)

possibly, plague. The mouth becomes foul, the tongue coated with dense brown fur, the breath offensive. Epistaxis is frequent in some epidemics, and vomiting may be a distressing feature. For the next twelve or fourteen days the temperature remains raised, with slight morning remissions, and the urine shows a faint cloud of albumin. As a rule the urea and chlorides are increased in amount.

The rash appears on the fifth day, first upon the abdomen and inner aspect of the arms, spreading over the chest, back and trunk, rarely involving the face; it is generally pleomorphic. The term "mulberry rash" has been used to describe the features of the exanthem, but it really consists of roseolar macules, together with a fine irregular dusky mottling underlying the epidermis and generally termed "subcuticular mottling"; it may become petechial, and involve palms of hands and soles of feet. (Plate IX, Fig. 3.) Exceptionally the rash, instead of being a mixture of purple and copper, is bright red; it may be hæmorrhagic. It fades slowly and may

persist for ten days. After the appearance of the rash, prostration and cardiac weakness become pronounced.

In brown- or dark-skinned natives, a typhus rash may be very difficult to discern; to make the subcuticular mottling visible thorough cleansing of the skin and a good strong light are often necessary. Congestion of the arm by means of a tourniquet may render the petechial spots more distinct, a method which has been practised with success in the early diagnosis of the rash in Europeans. In natives the rash is often most pronounced round the umbilical region.

When a typhus epidemic attacks an isolated population, as for instance in a desert oasis, terrible complications due to sepsis and neglect may ensue; in such circumstances terminal broncho-pneumonia is very common. In the survivors from an attack there may be extreme emaciation, as well as implication of the nervous system—ataxia, violent tremors, mania or dementia. Abortion in pregnant women is common. The young and the aged readily succumb. Parotitis and noma are frequent complications. Relapsing fever and typhus may often coexist. Constipation rather than diarrhœa is the rule, and the mouth becomes very foul, the lips and teeth being covered with sordes. Bedsores are a frequent complication.

On the appearance of the rash there may be signs of bronchitis, and, the mental lethargy becoming more pronounced, the patient sinks into the "typhus" state. Cerebration is slow; hands and tongue are tremulous; the patient is difficult to nurse, and emits an odour which has been compared to "gun-washings," or that emanating from a cupboard containing well-blacked boots. The odour may not always be distinguishable. In the second week a low muttering delirium supervenes, and the secretion of urine may be diminished or even suppressed. The spleen may be enlarged. Often symptoms of cortical irritation, such as muscular twitchings and incontinence of urine, may be observed.

As the fourteenth day approaches, signs of improvement may set in and the temperature suddenly fall by crisis, or sometimes by rapid lysis. If a fatal issue is to ensue, it generally occurs about the twelfth or fourteenth day, or later, when the temperature is subnormal, from exhaustion or cardiac failure. The blood picture shows nothing definite, though there is usually a moderate leucocytosis of 12,000 to 15,000.

During convalescence the greatest care should be taken against exciting the heart.

Diagnosis.—Typhus in early stages is apt to be confused with measles, typhoid, relapsing, or cerebro-spinal fever, or with subtertian malaria. In an epidemic there is rarely any doubt. The more gradual onset of the fever and the less marked stupor, together with a negative hæmoculture, differentiate typhoid. The other conditions mentioned which may simulate typhus may be readily differentiated

by laboratory diagnosis. It is said that plague presents the same picture of alcoholic-like intoxication as does typhus, but in the former there is no rash. Influenza of acute onset, such as the epidemic of 1918, may simulate typhus in its early stages. The rashes of Japanese river fever and of the spotted fever of the Rocky Mountains have many features in common with typhus, but difficulty in diagnosis is liable to arise only in the restricted areas in which those fevers occur.

The *Weil-Felix reaction*, first discovered by Wilson of Belfast, is a very real aid to the diagnosis of typhus. A bacillus, *Proteus vulgaris*, now termed X 19, originally isolated from the urine, where it was originally regarded as a contamination, possesses in emulsion the extraordinary property of being agglutinated by typhus serum as early as the fifth day of the disease. The test may be performed in test-tubes by the progressive dilution method, or with Garrow's agglutinometer (p. 1036). By the latter method an agglutination of 1 : 20 may be regarded as diagnostic. The maximum agglutination results are obtained from the eighth to the twenty-first day; a titre of 1 : 2500 has been recorded; the reaction may be obtainable for sixty days. Occasionally typhus serum may co-agglutinate cultures of *B. typhosus*.

The appearance, in the blood of typhus cases, of agglutinins specific for X 19 is not accompanied by the formation of specific immune bodies, though the latter are produced when a normal person is injected with cultures of X 19. Using an emulsion of this organism as an antigen, a positive complement-deviation reaction may be obtained with the serum of the inoculated subject.

There is little evidence, either from systematic blood- and urine-cultures during life, or from the organs post mortem, that this bacillus (*P. vulgaris*), which can be cultivated in artificial media with ease, is the ætiological factor in typhus, but it most certainly must be regarded as a specific response of the infected organism to one of the biological phases of rickettsia organisms.

This reaction is now recognized as a specific serological diagnosis of true typhus, and its value has been realized in Mexico, Chile, Argentina, Peru, and Indo-China. The majority of typhus-like fevers will also agglutinate this organism. In the course of time serological variations of the original X 19 proteus strain have arisen, as for instance, the XK strain (Kingsbury), which has been found specific for the serological diagnosis of the rural type of tropical typhus.

Isolation of B. proteus.—According to Felix, this organism can be isolated from the blood and organs in typhus. Ten cubic centimetres of blood is taken in the first few days of the fever into each of 5 or 6 small tubes; the blood is allowed to coagulate and the serum poured off till the clot is free. Some of the tubes are put into the incubator at 37° C. Loopfuls of blood are taken daily from the centre of the clots and inoculated on to serum-broth and serum-agar. This process is continued for ten days and then the broth is poured into the tubes containing the blood-clot, and they are incubated and sub-cultures taken for several weeks.

From the urine.—This is collected in sterile tubes, centrifuged, and the sediment washed. Loopfuls of this are inoculated into serum-broth tubes and into serum-agar and incubated.

From the organs.—Small portions of organs obtained post mortem are placed in sterile tubes, and loopfuls of these removed from day to day and inoculated into serum-broth tubes and incubated.

An intradermal test has been devised by Giroud (1938). The serum of the patient is mixed with a definite dose of the virus (an emulsion of the tunica of the guinea-pig infected with the murine strain) and injected into the skin on the inner surface of the thigh of the rabbit. A mixture of normal serum is used as a control. If the patient has, or has had, typhus, no reaction will appear, whereas on the control side a marked reaction occurs.

Treatment.—As there is no specific drug for typhus, special care must be devoted to nursing. Strict attention must be paid to the hygiene of the mouth. The recumbent position is absolutely essential. Bedsores should be guarded against. It is equally essential that the patient have as much fresh air as is possible. Stimulants must be given to maintain the cardiac action, the favourite being port wine; but care must be exercised that it is not given, as is so often the case, in excess—8 oz. in the twenty-four hours is sufficient. Tincture of digitalis, digitalin (gr. i), or digitoxin (digitaline crystallisée, gr. $\frac{1}{100}$) are indicated as cardiac stimulants. Lumbar puncture may be employed to relieve the delirium and other cerebral symptoms; as a rule there is excess of pressure in the cerebro-spinal fluid. There are no special precautions with regard to diet, which should be nutritious and easily digestible.

Serum treatment has been introduced in epidemics in Southern Russia by Asheshov. The serum itself is obtained from patients during convalescence after the temperature has been normal for a period of four to eleven days. When injected in doses of 20–50 c.c. it is said to mitigate the severity of the symptoms, though it does not shorten the course of the disease. This method is applicable to a limited number of cases during an epidemic.

Mühlens reports that two intravenous injections of *novasurol* (1 c.c. of a 10-per-cent. solution) appear to cut the fever short. There is some evidence that sulphanilamides exert a therapeutic action.

Prophylaxis.—This consists almost exclusively in the destruction of body-lice. The body should be shaved—including the pubes and axillæ—and the hair of the head cropped. After a cresol bath the underclothing should be smeared with a preparation consisting of unwhipped naphthaline 4 parts, soft soap 1 part; but whenever possible all clothing, including blankets and bedclothing, should be disinfected, preferably by dry heat. To kill lice and their eggs with certainty, a temperature of 55° C. for 30 minutes, or of 60° C. for 15 minutes, is required. Disinfestation of clothes on a large scale may be accomplished on the railway in luggage vans, by closing the doors and turning on superheated steam from the engine. The use, under field conditions, of the Serbian barrel, in which the clothes are saturated with steam under pressure from water within the barrel itself, is a practical method. In default of steam, ironing of the seams of the clothing has been found useful. Soaking in 2-per-cent. lysol, or in dettol, destroys both the pediculi and their eggs.

Prophylactic inoculation.—Several methods of active immunization

against louse-borne typhus are at present in use in various parts of the world :

(1) Vaccine prepared from the contents of the intestine of infected lice (killed virus) is known as Weigl's method, and can be obtained from Professor R. Weigl, Institute of General Biology, Lwow, Poland. Also from the Director, State Institute of Hygiene, Warsaw, Poland.

(2) Vaccine made from rickettsiæ of the murine type of typhus virus, grown either in the rat, or in tissue-culture, is recommended by Zinsser (killed virus). It can be obtained from Professor Hans Zinsser, Harvard University Medical School, Boston, U.S.A.

(3) Vaccine containing living attenuated virus of the murine type (Nicolle and Laigret). It can be obtained from the Director, Institute Pasteur, Tunis.

The most efficient is undoubtedly Weigl's vaccine, but it is difficult to prepare in large quantities. Shahin has published (1935) the results of inoculation of 183 persons with this vaccine ; only two showed a rise of temperature and no cases of typhus occurred in those inoculated. Nicolle and Laigret describe their vaccine which is made from the virus obtained from ground-up brains of infected guinea-pig and rats. The material is emulsified in egg-yolk and suspended in oil. Of 110 persons who were inoculated all were found to be subsequently immune to a test dose of the historic virus.

Blanc (1936) states that 11,216 persons have been vaccinated with living bile-treated typhus virus by himself and his colleagues. The injected guinea-pigs are killed on the spot. Emulsions are made from the *tunica vaginalis*, spleen and suprarenal glands. Ox-bile in a strength of 5 per cent. is added to the emulsion and allowed to act for fifteen minutes ; then 1 c.c. of the vaccine is inoculated under the skin.

The material obtained from one guinea-pig suffices to inoculate a thousand persons. Out of 8,234 persons inoculated in one day, three developed a fever in the first twenty-four hours. No cases of typhus were noted amongst those thus inoculated.

II. FLEA TYPHUS—BRILL'S DISEASE OR ENDEMIC TYPHUS

Described originally by Brill in New York, this form of typhus was looked upon as a particularly mild or "larval" form of the epidemic or true typhus ; but it was sporadic in nature and is definitely not carried by lice or spread in a manner peculiar to louse-borne typhus.

From 1912 onward it has been shown that between the virus of true typhus and that of Brill's disease a cross-immunity exists, so that the latter came to be regarded as the *inter-epidemic* form of true typhus. It has also been shown that lice can be infected by anal injection with the virus of Brill's disease by Weigl's method and that rickettsia appear in the cells lining the midgut of these insects, exactly as occurs in true typhus. On epidemiological grounds the association of endemic typhus with rats and grain stores was

suggested by Hone (1922) in Australia, and again by Maxcy (1926) in America; in 1931 experimental proof was provided by Mooser, and by Dyer and his collaborators, that the rat was the reservoir and the rat-fleas (*Xenopsylla astia* and *X. cheopis*) were the carriers of the virus. Rats were collected from the areas where numerous cases of endemic typhus had occurred. On chloroforming them, the fleas were collected, emulsified and injected intraperitoneally into guinea-pigs. After four days' incubation-period these animals reacted with fever and swelling of the testes, and exactly the same reaction follows injection of virus of epidemic typhus (Neill-Mooser reaction).

In the same year Mooser, Castañeda, and Zinsser in Mexico demonstrated the presence of endemic typhus virus by injecting guinea-pigs with the brain-emulsion of rats caught in the endemic area. Also Dyer and his collaborators demonstrated that *X. cheopis* fleas become infected when fed upon infected white rats, and can convey the infection to other rats, and further, that the virus multiplies in the body of the flea, and that the fæces of this insect are infective and Rickettsia bodies can be demonstrated in them. Brumpt and other workers in Europe (1932) have confirmed Dyer's results. Zinsser has shown that the classical, or *human virus*, and the rat virus are two varieties of the same species which resemble one another in their antigenic properties, but are *not* identical. He has never succeeded in transforming *permanently* the classical human virus into the *rat* virus.

Apparently Brill's disease is comparatively common in Palestine. During 1927 there were 85 cases with one death. Most of the patients came from the farming population.

It may be asked why this form of typhus does not spread as plague does, considering the close connection between the rat and man. The answer is that the virus does not remain active in the rat for many days and that this animal does not *die* of the disease as in *B. pestis* infections, hence the flea population is not forced to seek an alternative host as in plague.

The relation of endemic to epidemic typhus can now be explained by the experimental work recorded above. Louse-borne typhus spreads in epidemics directly from man to man, as no other animal host is necessary. The infected lice are driven from the body of the infected person either by the high temperature of the body or by the death of the patient.

The lice in epidemic typhus have been shown to be heavily infected with rickettsia, but the *X. cheopis* flea in endemic typhus does not by any means show such a heavy infestation.

The difference in the vectors of these two diseases also probably accounts for the fact that true typhus is a disease of the winter months and of crowded and insanitary peoples, whereas Brill's disease occurs in warm weather, is not associated with crowded humanity, and is definitely associated with rats.

Other forms of typhus resembling Brill's disease have been described in Australia and in North and South Africa, whilst the ship-fever of Toulon (*fièvre nautique*) appears to be a local form of it. It is also possible that the forms of *trench fever* with a rash which was definitely

transmitted by rickettsia-infected lice (*R. quintana*) come into this group. It has been pointed out that in trench-fever-infected lice the rickettsia were found lying free in the lumen of the alimentary canal and were not enclosed in the epithelial cells lining the midgut as are the rickettsia of true typhus.

The particular variety of tropical typhus (*see* p. 269) described by Fletcher and his colleagues in Malaya as the urban type (W. form) occurring in towns, and spreading amongst those engaged in the grain trade, probably belongs to this same group.

III. TICK TYPHUS (*Fièvre Boutonneuse*)—TICK-BITE FEVER

Synonyms.—Marseilles fever; Eruptive fever: *fièvre exanthematique;* Tick-bite fevers, South African, Indian and South American forms.

First described by Conor and Bruch in 1910 in Tunis as "*fièvre boutonneuse,*" this typhus disease has been known to occur on the Mediterranean littoral and was later shown to exist also in Marseilles and many other districts in Southern France, as well as in Italy (Carducci), Portugal, Spain, Greece, and Roumania. It has now been reported by Blanc from the Guinea Coast and by Peltier, Carrière and others from Senegal, while Gordon and Davey (1936) have discovered a form in Sierra Leone. It was formerly thought to be Brill's disease, but can be differentiated from it on clinical grounds and also by the Weil-Felix reaction, which was at first considered to be negative in *fièvre boutonneuse.* The distinctive features of this fever are that the virus is transmitted by the common dog-tick, *Rhipicephalus sanguineus* (Durand, Conseil and Brumpt, 1930), and that the dog constitutes the reservoir of the virus, for these animals have been shown to be susceptible and their blood has been proved to be infective both for man and monkeys (Durand). Another distinctive feature is the appearance of the primary sore at the site of the infecting tick-bite, which becomes gangrenous and is known as "*tâche noire*"; it varies in size from a pin's head to a pea, and it is not usually painful. Lymphangitis subsequently occurs, and this phenomenon is comparable with that seen in tick-bite fever in South Africa (Troup and Pijper, 1931), and in Japanese river fever. French investigators have hesitated to include it in the typhus group on the grounds that the Weil-Felix reaction—X19—is negative, and reactions in the inoculated guinea-pigs differ.

The Neill-Mooser reaction in guinea-pigs has not been obtained, but in 1932 Caminopetros, in Greece, showed that, if an emulsion of infected ticks is injected into guinea-pigs, these animals react in the same manner as when an emulsion of infected *X. cheopis* fleas are used in Brill's disease, *i.e.* fever and scrotal reaction. It has further been shown that the Weil-Felix reaction X19 is really positive, and that the virus of Brill's disease does not protect a monkey from the virus

of Marseilles fever and *vice versa.* So it can be definitely stated that "*fièvre boutonneuse*" is merely a local variety of tick-borne typhus.

Tick-bite fever was originally described in South Africa by McNaught in 1911. It has been redescribed by Pijper and Dau in Pretoria in 1934. This form closely resembles *fièvre boutonneuse,* but is conveyed by larval ticks—*Amblyomma hebræum*, *Rhipicephalus appendiculatus* and *Boophilus decoloratus.* The small ticks climb on to grass and attach themselves to man or animals and, being veld dwellers, are therefore not found in houses or on domestic animals, and in this respect the disease resembles Rocky Mountain fever. Rickettsia can be demonstrated in the Malpighian tubules of infected ticks, whilst an emulsion produces the disease in man and animals, and a rising titre of agglutination for Proteus-X strains. In nature, infection is conveyed by tick-bite.

Two forms of this fever are met with—the mild, or abortive, and the fully-developed form. In the first, the only symptom noted may be the presence of a primary sore at the site of the bite, accompanied by a local lymphangitis. In the fully-developed form the fever lasts for eight to ten days, with a primary sore, severe headache, appearance of a rash on the fifth day, stiffness of the neck, and conjunctivitis (Plate VIII, 3). This fully-developed form has been confused with meningitis, with measles and with typhoid fever. The serum reactions are not quite clear-cut ; there is a definite Weil-Felix reaction to all three variations of Proteus X. In most cases O.XK was agglutinated in a higher titre than O.X19. Guinea-pigs inoculated intraperitoneally with patient's blood responded by a febrile reaction and slight scrotal swellings. They became immune to the virus of epidemic typhus. Gear and Bevan have reported similar cases from Johannesburg, and this is apparently also the form of sporadic typhus found in Kenya. Gear and Douthwaite regard the dog as the reservoir of infection in Cape Colony, and suggest that the dog-tick *Hæmaphysalis leachi* may act as a vector in that district.

In India, McKechnie in 1911 described a mild sporadic form of typhus in the Kumaon Hills in the North-West Frontier district, and in 1916 Megaw himself suffered from an attack which he attributed to the bite of a tick. Since then, others have been described by Stott (1935) in Lucknow. The serum agglutinates O.X19 in a high dilution. The exact species of tick vector is unknown.

Similar tick-borne typhus cases have been described by Hone in Australia (1922), by Maxcy in the United States. The distribution of sporadic tick-borne typhus thus appears to be a very wide one.

South American form.—A form of tick typhus appears to be quite common in Brazil, and apparently resembles *fièvre boutonneuse.* The rat is again the reservoir of the virus, as has been described by Montiero. He has succeeded in transmitting the virus through the tick *Amblyomma cajennense,* and has produced intraocular lesions in guinea-pigs and monkeys by the injection of

the virus from the blood ; and it has been possible to demonstrate the presence of Rickettsia in the endothelial cells of Descemet's membrane. Fialho (1932) states that in this form the Weil-Felix reaction with X19, X2 and XK is usually present in low dilutions.

Dias (1938) states that the natural reservoir hosts are the opossum, the domestic and wild dog (*Canis brasiliensis*), the wild rabbit (*Silvilagus minensis*), and the agouti (*Dasyprocta*). Vectors are several species of *Amblyomma*, viz., *A. cayennense*, *A. striatum* and *A. brasiliense*.

IV. TICK TYPHUS—ROCKY MOUNTAIN SPOTTED FEVER

Synonyms.—Rocky Mountain Fever; Black Fever; Blue Disease.

Definition.—A specific fever supervening on the bite of ticks—*Dermacentor andersoni* (and *D. variabilis*)—and resembling, symptomatically, classical typhus.

History.—For upwards of forty years a peculiar disease, variously named "spotted fever," "blue disease," "black fever," had been recognized as endemic in limited districts of Montana, Idaho, and Wyoming, America. Wolbach described in 1919 a rickettsia body as the germ-cause of the disease. In 1906 King ascertained that the disease supervened on the bite of *Dermacentor andersoni* (*D. venustus*)[1] (Figs. 290, 291, pp. 976, 977). In the eastern borders of its range the vector is *D. variabilis* (the common dog-tick of North America).

Geographical distribution.—The disease has been reported from several of the western states of the American Union—Idaho, Montana (Bitteroot Valley), Wyoming, Utah, Nevada, Oregon, Colorado, and Washington States. Recently it has been realized that it is spreading eastward and is now reported from North and South Carolina. It is believed to occur also in the Alaska Territory, and in 1916 was definitely proved by Kelly and Cumming to exist in North California. It is found principally in valleys and near the foothills of mountains in sharply defined and limited areas. It attacks any age and either sex, and is not directly contagious.

Ætiology.—The evidence is now conclusive that the germ (*Rickettsia rickettsii*) of Rocky Mountain fever is introduced by the bite of *D. andersoni*, locally known as the "wood-tick." It is only the adult tick that attacks man (*see* p. 976), who is very susceptible to infection, as is shown by the numbers of scientists who have fallen victims to it (Brumpt in Paris became accidentally infected with this virus in his laboratory). The Rocky Mountain goat, the domestic sheep, black bear, coyote, badger and lynx also serve as hosts to the adult ticks, but the larval and nymph stages develop principally on the ground squirrel, *Citellus columbianus*, and the woodchuck, *Marmota flaviventer*.

[1] The names *D. venustus* and *D. andersoni* refer to the same species. The differences in the nomenclature of the tick used by various authors have resulted in a good deal of confusion. *D. reticulatus* and *D. occidentalis*, apparently distinct species, have at various times been incriminated as carriers of the infection. *D. variabilis* is the eastern representative.

The disease occurs in the spring months (March to July) at a time when *D. andersoni* and *D. variabilis* are prevalent.

The Columbian ground-squirrel lives amongst birch woods where it digs its burrows. It hibernates in winter and apparently in this state harbours the virus of Rocky Mountain fever. The woodchuck is really a marmot and is about 2 feet in length. It hibernates in deep burrows over 50 feet in length during the winter.

Wolbach noted small bodies staining with Giemsa in the endothelial cells of the blood-vessels and in the testes of man and of virus-infected guinea-pigs, as well as a general distribution of the rickettsia organisms in the bodies, salivary glands, and eggs of infected ticks (*Dermacentor*). Two morphological types are recognized: one a lanceolate diplococcal organism found in the circulating blood as well as in the endothelial cells, and containing chromatin-staining substance; the other staining blue, and rod-shaped. Originally known as *Dermacentroxenus rickettsi*, the organism is now known as *Rickettsia rickettsii* (Fig. 38). In conjunction with Schlesinger, Wolbach has cultivated

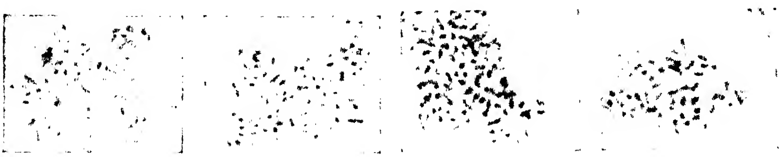


Fig. 38.—Photomicrograph of *Rickettsia rickettsii*. × 2,000. (*Dr. A. C. Coles.*)

the organism in the tissue-plasma of guinea-pig testis, when numbers of filamentous forms of the organism develop in the endothelial cells of the vessel-walls.

Noguchi cultivated from the intestinal tract of *D. andersoni* a bacillus, *B. rickettsiformis*, which resembles the pathogenic *Rickettsia*.

According to Ricketts, the virus is easily inoculated into man, and can be passed through an indefinite series of monkeys and guinea-pigs, giving rise in them to the characteristic symptoms, in which a scrotal swelling is held to be pathognomonic. Immunity is conferred upon these animals, showing the close relationship of the typhus group. Dyer has demonstrated that a crossed immunity exists between the virus of the South American typhus, Rocky Mountain fever, and the virus of *fièvre boutonneuse* (Badger). The larva, nymph, and adult male and female tick are all of them efficient intermediaries for the parasite. Dyer and others have shown that the rickettsia is transmitted through the egg of the infected tick to the larva in a hereditary manner. Ricketts suggested—seeing that in one place (Montana) the case-mortality in man is as high as 90 per cent., whereas in another place (Idaho) it is only 5 per cent.—that there were two different species of tick capable of carrying the infection; in the former instance it is *D. andersoni*, in the latter *D. variabilis*. The proportion of ticks infected under natural conditions is small—only 1 in 296 in Ricketts's experience.

In conformity with the seasonal prevalence of the tick, the disease in man is most frequent in April, May, and June.[1]

Parker (1933) has shown conclusively that under natural conditions the infection is kept going amongst susceptible rodents by *D. variabilis*, the dog-tick, and *Hæmaphysalis leporis*, the rabbit-tick. The latter does not bite man. After the ticks have fed there is a period of *invasion* which may last 12 days: the blood virus becomes changed into the "*tick virus*."

Pathology.—Post mortem, in addition to the skin lesions, there are marked hypostatic congestion of the lungs, subserous petechiæ, softened myocardium, enlarged firm spleen and lymphatic glands, fatty degeneration of the hepatic cells, and congestion of the cortex of the kidneys. Constant lesions, both in man and in animals, are hæmorrhages into the genitalia; gangrene of the prepuce and scrotum are often noted. Proliferation of the endothelium of the arteries and veins of the skin and subcutaneous tissues, with accumulation of rickettsia bodies, is a feature, the cells taking on phagocytic properties and ultimately becoming necrotic. There is a perivascular mononuclear infiltration, as in typhus.

Symptoms.—A short period of malaise is followed by chills, which are repeated with diminishing severity at irregular intervals throughout the attack. By the second day the temperature has risen to 103° or 104° F., and by the fifth day to 105° or 107°. A typhoid-like condition, with low muttering delirium and semi-consciousness, is rapidly developed. If the patient is to recover the temperature begins to fall about the end of the second week, fever subsiding usually by lysis.

About the fourth to seventh day an eruption appears on the wrists, ankles, or back, extending rapidly to the trunk, scalp, hands, and feet. At first it consists of minute rose-coloured spots; these soon assume a petechial character and, spreading, tend to become

[1] **Tick Paralysis.**—According to Hadwen, the tick, *D. andersoni*, as it occurs in the dry district of British Columbia, Keremeos, gives rise to a peculiar form of paraplegia in sheep, which, directly or indirectly, may prove fatal. In the same district it affects man and other animals in a similar way. Todd has called attention to this disease, of which he has collected a considerable number of cases, some of them fatal, caused by the bites of this species as well as of *Hæmaphysalis cinnabarina*. Nuttall, working at Cambridge, England, confirmed Hadwen's experiments. He placed one of the ticks received from Hadwen on a healthy dog. Twelve days afterwards it became completely paralysed in fore and hind legs, and gradually recovered. According to these authors, a similar disease is produced in South Africa by the bite of *Ixodes pilosus*.

Pijper and Dau have also described a tick-bite disease in South Africa, and a similar type occurs in Sumatra and is known as the pseudo-typhus of Deli, showing a primary cutaneous sore with enlargement of regional lymph glands.

This form of tick disease is manifestly different from Rocky Mountain fever, as it is nonfebrile, is unattended with eruption, and is not communicable by inoculation. Possibly it is produced by a poison instilled by the tick during haustellation. The wound it makes is very painful, is attended with œdema and, on forcible removal of the tick, with free bleeding as if some anti-coagulin had been introduced. The symptoms of the disease suggest infantile paralysis.

In sheep, the favourite points of attachment of the tick are on the back along the course of the spine; in man, the nape of the neck.

A somewhat similar form of paralysis is described by Eaton and Dodd as following on tick-bite in Queensland, the incriminated ticks being *Ixodes ricinus* and *I. holocylus*. Bancroft reported from the same country similarly-caused epileptiform convulsions in cats and dogs.

confluent, especially on the more dependent parts of the body and limbs. In other instances the spots remain discrete, and are brownish or purplish in colour, giving to the surface of the body a speckled appearance. A certain amount of icteric tinting of skin and scleræ is also present. During the third week desquamation sets in, the eruption fading as fever subsides. In some cases the skin of the elbows, fingers, toes, lobes of the ears, etc., becomes gangrenous.

Constipation is usual. The liver is slightly enlarged, the spleen markedly enlarged and tender. The scanty, high-coloured urine may contain albumin and casts. Early in all severe cases there is œdema of the face and limbs. Nausea and vomiting set in about the beginning of the second week, and persist in fatal cases. Respiration is rapid. Slight catarrh of the respiratory tract is present throughout ; the pulse loses in volume as it increases in frequency. There is but little diminution in the blood-count, and only a feeble leucocytosis—12,000 to 13,000 ; the hæmoglobin is slightly diminished.

Complications such as gangrene of the tonsils, scrotum, and prepuce are more common in the milder type of the disease, as seen in Idaho. One attack of the disease confers immunity, and no instance is known of a second attack of this fever in man.

Diagnosis.—The sudden onset, the joint pains, and the negative Widal reaction differentiate this fever from enteric ; the geographical distribution is the most important factor in differentiating it from typhus. It was formerly thought that the Weil-Felix reaction-X19 was negative (Kelly), but it has now been shown that with different antigenic strains of the organisms this reaction becomes positive. On injection of infected blood into guinea-pigs the Neill-Mooser reaction of swelling of the testes and scrotum occurs as in true typhus (*see* p. 255), but further investigations are required as to whether any means of differential diagnosis can be obtained on these lines.

A differential table is given by Cumming and Milam for Rocky Mountain fever and Brill's disease :

Rocky Mountain Fever	Brill's Disease (Endemic Typhus)
Rural	Urban
History of tick bite.	Premises infested with rats.
Children attacked.	Adults and middle-aged.
One or two cases in the same family.	Sporadic.
Clinical :	
Sudden onset.	Onset sudden.
Fever up to 107° F.—lasts weeks and ends by lysis.	Fever lower. Crisis end of second week.
Rash on wrists, then general including palms of hands and soles of feet.	Rash first on trunk, flexor surface of limbs, rarely on face, palms or soles.
Mortality 25 per cent.	Mortality under 5 per cent.

In Colorado a milder form of Rocky Mountain fever is known as "Colorado tick fever" (Parker, 1937).

Treatment and prophylaxis.—In the absence of a specific remedy, treatment must be conducted on general principles, regard being had to the natural history and character of the disease. Intravenous injections of *mercurochrome 220 soluble* have been tried in 1-per-cent. solution. Recent reports from American sources speak favourably of sulphanilamides—*Prontosil album*—1·5 grm. daily, in controlling the duration and severity of the fever. Attempts at prophylaxis are now being carried out, based on the above-described mode of transmission. War is being waged on the ground-squirrel and the woodchuck; domestic stock and goats are being systematically dipped to prevent the spread of and, if possible, to exterminate the tick. It should be borne in mind that *D. andersoni* does not infest human dwellings.

Frick, finding that *D. andersoni*, when placed on the fleece of an unshorn sheep, either dies or remains unimpregnated, and is manifestly on an uncongenial host, suggested, in addition to the measures just mentioned, turning the badly-infected districts into sheep-runs.

Those who work in endemic areas should provide themselves with a working costume consisting of one piece; the trousers should be tucked up inside woollen socks, and the sleeves at the wrists secured with a strap. Tick-bites should be cauterized or excised.

Prophylactic inoculation.—Parker has published the results of ten years' observation. The tissues of virus-laden adult *D. andersoni* are emulsified in formol-phenol-saline, and for this purpose 500 ticks make 400 c.c. of vaccine. Each batch has to be standardized by protection tests with guinea-pigs, and the dose is estimated at 1 c.c. for children and 2 c.c. for adults. It is concluded that the vaccine has a definite prophylactic value, and in Montana the inoculated had mild attacks and recovered, whilst the uninoculated died. In ten years up to 1934, 150,000 had been inoculated, and of these 64 developed the fever. In the Bitteroot Valley the mortality in uninoculated adults was 82 per cent.: in the inoculated, 6·6 per cent.

V. MITE-TYPHUS, TROPICAL TYPHUS, JAPANESE RIVER FEVER

Synonyms.—Tsutsugamushi; Shimamushi; Kedani Mite Disease; Exanthematous Glandular Fever; Scrub Typhus, "K form."

Definition.—An acute endemic disease running a definite course, and attended with a considerable case-mortality varying from 10 to 52 per cent. It is characterized by the presence on the skin of an initial eschar, supervening on the bite of a species of *Trombicula*, or mite. This is followed by an ulcer, lymphangitis, fever, a peculiar eruption, bronchitis, and conjunctivitis. In all probability further research on crossed-immunity tests in this, Rocky

Mountain fever, and allied diseases will show that they are similar in many ways.

History.—This disease was first described by Palm in 1878, and subsequently, more fully, by Baelz and Kawakami. Ancient records indicate that it has been known for more than a thousand years. In 1925, cases of typhus fever occurred in a military camp in Kuala Lumpur in the Malay States; these were investigated by Fletcher, who, from a study of them and subsequent cases, was soon able to show that two forms of mild typhus existed in the Federated Malay States. The one was known as the *urban* type (W form), which occurs in the towns and spreads among the people who are handling grain, while the other form, which is now known as "*scrub typhus*" (K form), occurs in the country, especially on plantations, and has a close connection with the clearing and pruning of palm trees. Subsequently it was found possible to separate these *two diseases serologically.* Delbove and his co-workers have described a similar disease in Cambodia (1938) and in Indo-China.

Hatori published (1919) a very full account of the epidemiology, while Hayashi described minute intracellular bodies in the endothelial cells resembling rickettsia bodies.

Geographical distribution and epidemiology.—Formerly it was thought that tsutsugamushi was confined to the banks of two rivers on the west side of the island of Nippon, Japan—the Shinanogawa and one of its tributaries, and the Omonagawa. Every spring these rivers inundate large tracts of country, and later in the year hemp is raised on strips of the inundated district. The crop is reaped in July and August, and it is solely among those engaged in harvesting and handling this that the disease occurs. It is not communicable by the sick to the healthy. It now appears that the disease is widely spread in Formosa, and possibly in Korea, both among the Japanese settlers and the aborigines. In Formosa it occurs in the highlands as well as in the coastal plains. The epidemic commences in April and disappears in November. It has now been reported on certain estates in Malaya and an analogous fever has been described as "pseudo-typhoid" in Sumatra by Schüffner, and is carried by mites, *Trombicula deliensis.* The Mosman fever in Northern Queensland is of the same nature, as also in the Philippines, Malaya, and Indo-China, where it is known as scrub typhus.

In Malaya the urban disease (W form) is probably the same as Brill's disease or endemic typhus (flea-borne typhus), while in "scrub typhus" the actual vector is a mite. A complete study of this subject has recently been published by Anigstein (1933). In this form it is now possible to make the following positive statements: in contradistinction to what is found in *true typhus,* guinea-pigs and rats inoculated with tropical typhus (K scrub) virus, show a febrile reaction in only a small proportion of cases; but in those guinea-pigs which do not show such a reaction, the specific infection can be recognized by a loss of body-weight and by a swelling of the scrotum, while rickettsia-like organisms can be demonstrated in the tunica vaginalis of experimentally-infected guinea-pigs and rats (Neill-Mooser reaction). Rabbits and rats inoculated with human, or *passage,* virus of tropical typhus produce agglutinins of the O type against strains of *B. proteus.* The strains of *Rickettsia* isolated from tropical typhus can be divided into three groups and *members of one of the groups* show biochemical properties characteristic of the *B. proteus* group. In most cases Anigstein found that the strains cultivated bore no *serological relationship* to *B. proteus,* although rabbits and rats, when inoculated

with these strains, developed a positive Weil-Felix reaction. Anigstein now regards these strains, including those of the *B. proteus* type, as *biological phases* of the causal organism of tropical typhus. The researches of this investigator have therefore brought much more closely into line than has been done by previous workers, the association of *Rickettsia* with typhus, and they go far to explain the apparent anomalies of the Weil-Felix reaction.

The organism of "tropical scrub" typhus is regarded as a local variety of *Rickettsia orientalis*. Wild rats, such as the common urban rat (*R. rattus diardi*), the rural rat (*R. rattus jalorensis*), and the house rat (*R. concolor*), collected from an endemic area, showed in 10 per cent. of cases a positive Weil-Felix reaction, and moreover the rickettsia of tropical typhus were demonstrated in the tunica vaginalis of wild rats in a proportion of these animals which gave a positive Weil-Felix reaction. It may, therefore, be regarded as conclusive that the Malayan rat plays the rôle of a virus reservoir of tropical *scrub typhus*. Lewthwaite and Savoor (1937) have carried this matter a stage further, and by means of elaborate and exhaustive cross-immunity experiments complete proof exists of the identity of scrub typhus and Japanese river fever, both by the intraocular and intradermal reactions in rabbits and in monkeys.

Ætiology.—The Japanese have always attributed this disease to the bite of an acarus (locally called *akamushi*—red insect), the larva of *Trombicula akamushi*[1] (formerly incorrectly known as microtrombidium akamushi), resembling *Leptus autumnalis* of Europe, and popularly known as the kedani mite or "patau" (Figs. 287, 288, p. 972). Men, women, and children are equally susceptible; from their occupation it is commoner in men. New arrivals in the endemic districts are said to be specially liable. One attack does not confer immunity, although it may render subsequent attacks less severe.

Scrub typhus is essentially a place disease, for the infection does not cling to man or his surroundings, but is found in the rank vegetation of certain limited localities. A striking example has been afforded by an oil-palm estate of 3,000 acres in Malaya, where the African oil-palm is cultivated, and where several cases have occurred in almost any month for six years. The infection does not appear to be generally distributed throughout the plantation, but is concentrated in those parts where young trees are being pruned of dead flowers, and the disease is found in those coolies whose work brings them into close contact with them, while those employed in other work are rarely infected. The vector is therefore a mite, as Gater has found that the dead palm flowers are infested by enormous numbers of *T. deliensis*. The ears of rats which live in the infected areas are also infested with these insects (*Trombicula deliensis* and *T. akamushi*). This disease is, however, not necessarily limited to oil-palm estates, but is associated also with the coarse grass which is used as fodder for cattle. The organism, *Rickettsia orientalis*, has now been found in the salivary glands of mites taken from infected field-mice.

According to Kawamura and his co-workers, the blood of patients is very infective in the incubation period of the disease. The minimum dose capable of infecting monkeys is 0·001 c.c. The infective agent is easily destroyed by heating at 55° C. for ten minutes.

Culture has been effected by Anigstein in a special broth medium consisting of diluted Hottinger broth. The patient's blood is taken at an early stage

[1] Also known in Japan as *Trombicula coarctata* (Berlese).

of the disease and is defibrinated by glass beads. The culture tubes are then inoculated with 3-c.c. quantities of the blood, and are afterwards incubated at 37° C. for 72 hours, and then at room temperature (26°–33° C.) for four to five days. During this period a greyish layer becomes apparent on the surface of the sedimented blood, consisting of white corpuscles, blood-platelets, and micro-organisms. Most of the strains cultivated from patient's blood consist of rod-shaped organisms of a characteristic structure, and resemble *Bacillus fusiformis*. These organisms have been isolated from human blood, urine, and brain, and also from infected rats and guinea-pigs. That these "coccoid" organisms are a stage in the life-history of *Rickettsia* is now considered possible.

Nagayo and his co-workers have succeeded in transmitting the virus by intraocular inoculation into the eye of a guinea-pig. The inoculum in each instance was the infected aqueous humour. Infective material can also be injected into the testicle of rabbits, in which it produces the characteristic reaction. Nagayo further claims that this rickettsia can be successfully cultivated in tissue-culture. For this purpose the endothelium of Descemet's membrane of the eye is used with normal aqueous humour and rabbit plasma. The inoculum, too, in this instance, is infected aqueous tumour. The mite occurs numerously on the ears of the field-vole, *Microtus montebelloi*, and other rodents—*Mus jerdoni*, *R. rattus rufescens*, *R. decumanus*, *R. agraius*—which, however, have not been found to be suffering from any particular disease at the time. It also becomes more widely distributed by the agency of a small warbler—*Acrocephalus orientalis*—domestic fowls, a pheasant—*Phasianus formosanus*—and a quail—*Turnix taigoon*. The mite will also attack dogs, cats, and the buffalo. Its life-cycle has now been worked out by Nagayo, Kawamura, and others, and it is known to be the hexapod larva of *Trombicula akamushi*, a red mite 0·9 mm. in length, living in grass, but which is non-parasitic in its habits. Recent work suggests that the virus of tsutsugamushi also occurs in the body-cavity of the adult mite.

In Sumatra and Malaya the vectors *T. deliensis* and *T. schüffneri* frequent the undergrowth and long grass known as "lalang" in clearings of the virgin jungle; they have been found also to infest the crow-pheasant (*Centropus javanicus*) which inhabits that kind of country.

T. deliensis is pale ochre in colour; *T. akamushi*, bright vermilion.

Nicolle and Sparrow carried out cross-immunity experiments, and it was found that the river-fever virus protected against itself, but not against true typhus, nor did the typhus virus protect against the river virus. In lice (*pediculus*) the river virus remains active for seven days after the infective feed, but cannot be conveyed by their bite; on the other hand it remains active in fleas (*X. cheopis*) for eleven days and *can* be conveyed by their bites.

Pathology.—The lesion at the site of the bite undergoes coagulation necrosis, and affects the epidermis, the corium, and the tissues surrounding the puncture. It is well marked off from surrounding tissues by a boundary line. The spleen is generally enlarged, the capsule tense, and the substance soft and friable; not infrequently areas of necrosis are present. The liver is enlarged, and shows cloudy swelling on section. The lungs are congested and frequently hypostatic pneumonia is present. The bone-marrow shows signs of great activity. There is a generalized enlargement of all the lymphatic glands, but those in the neighbourhood of the lesion are especially affected, and may attain the size of a pigeon's egg. The elements most affected appear to be the lymphocytes. Areas of patchy necrosis are frequently encountered.

Symptoms.—The person attacked by the mite does not usually notice the bite, and later only feels a pricking sensation when he happens to touch the spot. The mite, or mites, can easily be seen by the aid of a strong magnifying glass, with their heads and bodies buried in the skin, but only when they are carriers of the disease do any definite pathological changes take place round the lesions they inflict. After an incubation period of from four to ten days the disease usually begins with malaise, frontal and temporal headache, anorexia, chills alternating with flushes of heat, and prostration. Presently the patient becomes conscious of pain and tenderness in the lymphatic glands of the groin, armpit, or neck. On inspection of the skin of the corresponding lymphatic area there is discovered—usually about the genitals or armpits—a small (2 to 4 mm.) round, dark, tough, firmly adherent eschar surrounded by a painless livid red areola of superficial congestion. Occasionally two or three such eschars are discovered. Although a line of tenderness may be traced from the sore to the swollen, hard, and sensitive glands, no well-defined cord of lymphangitis can be made out. The superficial lymphatic glands of the rest of the body, especially those on the opposite side corresponding to the glands primarily affected, are also, but more slightly, enlarged.

Fever of a more or less continued type now sets in, the thermometer mounting in the course of five or six days to 104° or 105° F. The conjunctivæ become injected, and the eyes somewhat prominent; at the same time a considerable bronchitis gives rise to harassing cough. The pulse is full and strong, ranging rather low—80 to 100—for the degree of fever present. The spleen is moderately but distinctly enlarged, and there is marked constipation.

About the sixth or seventh day an eruption of large dark-red papules, tending to become confluent on the cheeks, and fading on pressure, appears on the face. It extends to the forearms, legs, and trunk, being less pronounced on the upper arms, thighs, neck, and palate. Simultaneously a minute lichenoid eruption breaks out on the forearms and trunk. This lasts usually from four to seven days; if but slightly marked, the eruption may fade in twenty-four hours, becoming pigmented.

During the height of the fever the patient is flushed, and at night, it may be, delirious. He complains incessantly, probably on account of a general hyperæsthesia of skin and muscles. Deafness is also a feature.

As the disease advances, the symptoms become more urgent; the conjunctivitis is intensified, the cough becomes incessant, the tongue dries, the lips crack and bleed, and there may be from time to time profuse perspiration. By the end of the second week—sooner or later according to the severity of the case—the fever begins to remit, the tongue to clean, and, after a few days, temperature falls to normal and the patient speedily convalesces. There is a well-marked leucopenia. The red cells are normal, but there is a decrease

in the coagulability of the blood. Bronchitis, diarrhœa, or diuresis may occur during the decline of the fever. The circular, sharp-edged, deep ulcer left after the separation of the primary eschar—usually during the second week—now begins to heal, and the enlargement of the glands gradually to subside. The urine is albuminous and gives the diazo-reaction.

Such is the course of a moderately severe case. In some instances, however, the constitutional disturbance is very slight, although the primary eschar may be well marked and perhaps extensive. On the other hand, the fever may be much more violent, and complications, such as parotitis, melæna, coma, mania, cardiac failure, or œdema of the lungs may end in death. Similarly, the duration of the disease varies according to severity from one to four weeks, three weeks being about the average. Relapses do not occur.

Pregnant women contracting tsutsugamushi mostly abort and die.

According to Hatori, reinfection may occur.

The death-rate in Japan is high—from 25–30 per cent., but much lower in Sumatra (0–15 per cent.).

Diagnosis.—As in other typhus diseases, the Weil-Felix reaction is of great service in diagnosis. As more investigations on this subject are proceeding, the meaning of the reaction is becoming more apparent (*see* p. 258). According to Felix, the serum of tsutsugamushi does not agglutinate proteus O. X19 or O. X2, but only O. XK. (Kingsbury strain), and the type of main antigen is therefore O. XK. The limited geographical distribution and seasonal incidence of the disease, together with the initial necrotic ulcer and lymphadenitis, should prevent any error in diagnosis. Plague may possibly be thought of in the first instance, but, even if a primary vesicle or ulcer exists in this disease, the matting together and exquisite tenderness of the lymphatic glands should put one on one's guard. Measles and dengue may also have to be differentiated.

Kuroda uses filtrates of O.XK for intradermal test for diagnosis. A positive result occurred after a period of two hours, during the first few days of illness, but after the sixth or seventh day a negative reaction resulted.

Treatment.—The site of the bite should be treated by cauterization or extirpation.

Recently stabilarsan in two doses of 01·5 grm. and 0·3 grm. at four days' interval has been employed with success. Lumbar puncture and the drawing off of fluid under pressure has also been followed by favourable results. Hayashi and Mukoyama have employed the serum of cattle and monkeys which have recovered from the disease ; in severe cases in which it was injected in the early stages, good results were claimed. Otherwise treatment is symptomatic only.

Prophylaxis.—In a mite-infected country all parts of the body should be properly protected. For this purpose a mite-proof suit has been devised by Hayashi and Nagayo. All articles of clothing

used in infected fields should be sterilized, and the parts of the body exposed to mite-bites bathed with Vleminck's solution. The most effective measure is the burning down of the bushes and grass in the endemic area before bringing it under cultivation.

Prophylactic inoculation.—Cultures from experimentally infected rats were used for this purpose by Anigstein in Malaya. When tested on rabbits they produced a positive Weil-Felix reaction in a dilution of 1 : 5000.

Forty-eight-hour cultures from agar slopes were emulsified in saline containing 0·3 per cent. formalin, and the vaccine was prepared in two strengths, namely, 200 million and 400 million organisms per c.c. Prophylactic inoculation on a large scale was commenced on the Palm-oil Estate in Malaya in 1930. Coolies received two injections at an interval of seven days, the doses being 200 million and 400 million organisms.

Amongst a series of nearly 300 coolies thus inoculated (1933) there appeared to be a marked diminution in the incidence of the disease. Since the date of attempted protection, there have been 48 cases, of which 19 belonged to the vaccinated and 14 to the unvaccinated groups. The conclusion is that the vaccine probably has some prophylactic value, but any consequent immunity is a fleeting one.

VI. "Q FEVER"

A new "fever entity" which was first noted in 1935 amongst workers in large meat-works in Brisbane, Queensland (apparently similar cases have occurred since 1933), has been studied by Derrick, Burnet and Freeman. Since that time some twenty cases have been described. "Q fever" does not appear to correspond with any classical type, although it has certain resemblances to members of the typhus group, but can be distinguished in various ways, particularly by the absence of a characteristic rash and a negative Weil-Felix reaction.

Epidemiology.—This is obscure and there is no obvious relationship to the season. Most of the cases occurred in meat-workers or dairy farmers.

Ætiology.—The virus is morphologically indistinguishable from the Rickettsia of true typhus and produces characteristic pathogenic effects on monkeys and mice. There is a well-defined febrile reaction during which the blood is infective for guinea-pigs and which follows the subcutaneous inoculation of the virus in the monkey.

On the other hand, mice inoculated intraperitoneally show enlargement of the spleen and liver with characteristic histological changes. Burnet has now obtained definite evidence that the causative organism is a Rickettsia, which can be cultivated on minced chicken embryo. The organism, *Rickettsia burneti*, reaches its maximum growth during the second week of culture. Additional evidence of the rickettsial nature of the disease is afforded by the finding of actual infection in bandicoots (*Isoodon torosus*) in Southern Queensland. This marsupial is susceptible to infection and in diseased animals the spleen is much enlarged. Several laboratory infections have occurred, and there is evidence that a mite, *Lyponyssus bacoti*, is responsible for transmitting the infection to human beings. Furthermore, the dog appears to be susceptible to infection with "Q" fever.

The virus is present in the blood of human cases, only during the fever period, and may also be present in the urine in later stages of the illness.

In sections and smears of infected mouse liver and spleen large numbers of rickettsia organisms are visible and occur in relatively large intracytoplasmic colonies.

Burnet and Freeman have found that the virus is filterable with difficulty through relatively permeable (0·7 μ) gradocol membranes and it survives on the chorio-allantoic membrane of the chick embryo.

An agglutination reaction of rickettsial suspensions by immune human, monkey and guinea-pig sera has been observed, and this reaction appears to be specific. The disease produced in the guinea-pig is mild and the mortality nil, but if the animal is killed during the fever, the spleen is found to be enlarged. One attack in the guinea-pig confers immunity, and this immunity has provided a means for diagnosis of " Q " fever. Rats are mildly susceptible, whilst albino rats and rabbits are resistant.

Symptomatology.—The onset of the illness is acute and sudden, and the course and duration of the fever vary. Sometimes there is rapid defervescence after six to nine days; sometimes the course is protracted to the third or fourth week and the temperature falls by lysis.

There is no rash as in true typhus. The outstanding symptom is headache and it may be severe and persistent, whilst the pulse-rate is slow. The disease is comparatively mild and there have been no fatalities.

Subsection D.—FEVERS CAUSED BY BACTERIA

CHAPTER XI

PLAGUE

Definition.—Plague is a specific, inoculable and otherwise communicable epidemic disease common to man and many of the lower animals. It is characterized by fever, adenitis, a rapid course, a very high mortality, and the presence of a specific bacterium, *Bacillus pestis* (*Pasteurella pestis*), in the lymphatic glands, viscera, and blood. In a large proportion of cases buboes form in the groins, armpits, or neck.

History.—The first authentic account of plague in Europe relates to an outbreak in A.D. 542, which, starting from Egypt, spread over the Roman Empire. The disease visited England as a widespread epidemic for the last time in 1664–79, and in 1664–5 upwards of 70,000 out of the 460,000 inhabitants of the London of that day perished. In those days it was known as the " Black Death " not, as popularly supposed, on account of the petechial nature of the disease, but on account of the " terrible death " it occasioned. In recent years, and from time to time, cases of plague have occurred in the Port of London in seamen from Eastern countries, and plague-infected rats are by no means uncommon in the docks of the metropolis ; but, with the exception of a limited epizootic in rats and rabbits, and several fatal cases in man in 1910 in Suffolk, there is no record of plague in Britain, apart from the cases occasionally seen in the seaports, since the seventeenth century. Plague reappeared in Paris in 1920 after an absence of three centuries.

Geographical distribution.—Probably plague is always present in some part of India and in Uganda, especially among the rude hill-people. It is known to have been endemic in the south-west of China, in the province of Yunnan, for many years. The present extension of plague probably had its origin in that part of China, and it is safe to prophesy that it will continue epidemic in that country for many years to come. Japan and the Philippines were both infected from China.

Imported from Hong Kong, the disease appeared in 1896 in Bombay, and subsequently as a great epidemic spread to Calcutta and to many other parts of India, where it still prevails. In 1913 plague spread from Negapatam to Ceylon, and in 1914 broke out in epidemic form for the first time in Colombo, where it remained confined

to one portion of the city. It may be said that India has suffered more than any other country; there have been years when the plague deaths exceeded a million. The highest death-rate was reached in 1907 when it was considerably above that figure, and it has been estimated that from the time of its introduction into India until that date there was a total of nearly ten million deaths.

Soon after its appearance in India, plague became extensively epidemic in Mauritius, and it still prevails there at certain seasons. Mombasa and British East Africa (including Nairobi), the West African colonies, Madagascar, Delagoa Bay, Cape Town, Port Elizabeth, and Durban, also Sydney and Brisbane in Australia, and Alexandria in Egypt, have all been invaded.

Until its appearance in Brazil, Argentina, and other South American countries, and in San Francisco and Mexico, plague had never invaded the Western hemisphere; now the plague question is of considerable importance in California. Peru, into which the disease was introduced from India in 1903, was the first country on the West Coast of South America to be invaded. The infection reached Ecuador through Guayaquil and raged at an altitude of 10,000 feet.

Epidemiology and endemiology.—*Age*, *sex* and *occupation* have very little influence in plague. The youngest children are susceptible.

Atmospheric temperatures, if very high or very low, seem to have a repressing effect. On the other hand, plague on more than one occasion has flourished during a Russian winter. On the whole, the evidence points to moderate temperature—50° to 80° F.—combined with a certain degree of dampness, as being the principal atmospheric condition favouring epidemic outbreaks and recurrences.

In large towns and in some districts in which plague recurs for several years in succession there is a seasonal periodicity (which may not be the same in all places) of maximum and minimum prevalence.

The *duration of epidemics of plague* is very variable. In large cities—Bombay, Hong Kong, Canton, for example—the disease when fairly established may not relax its grip for ten or more years. In smaller towns it may disappear in a few months.

The *extension of plague epidemics* is peculiar: the disease follows trade routes, and especially the grain trade. Sometimes it may spread rapidly from point to point; more generally it creeps slowly from one village to another, from one street or one house to another. Sometimes it skips a house, a village, or a district.

These and many other facts in the epidemiology of plague are to be explained by the connection of the disease with the rat and its flea, and depend in the main upon the migrations of the former and the breeding seasons of the latter.

Selvatic or wild rodent plague.—Formerly epidemiologists concerned themselves mainly in the study of rat epizootics, but more recently increasing attention is being paid to plague of wild rodents of the fields and woods, what is known as field-rodent, or selvatic, plague. It is

now realized that plague exists in a smouldering state over vast tracts of territory among the Asiatic marmots; among the "susliks," mice and jerboas of the desert region of south-eastern Russia; among the gerbilles and *muridæ* of the African high veld and coastal region; among the chipmunks and ground-squirrels of California; and in South America among the cavies and other peculiar rodents of the Pampas. Although field-rodent plague has given rise so far to comparatively little human mortality in most countries, this is not the case in North Manchuria, where the disease is endemic in the marmot or "tarabagan," from which source virulent epidemics of *pneumonic plague* have emanated.

The micro-organism.—The specific cause of plague is the bacillus which was discovered by Yersin and Kitasato in 1894. It occurs in great profusion in the characteristic buboes—generally in pure culture, although towards the later stages it is often associated with the streptococci and staphylococci of suppuration. It is present, besides, in great abundance in the spleen, intestines, lungs, kidneys, liver, and other viscera, and also, though in smaller numbers, in the blood, while in the pneumonic type of the disease it is found in the expectoration in enormous numbers. It may occur also in the urine and fæces; in the latter it may be hard to find by direct observation. Towards the termination of rapidly fatal cases it occurs in great numbers in the blood.

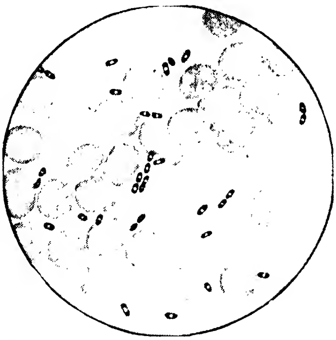


Fig. 39.—*B. pestis* **in peripheral blood in septicæmic plague.** × 500. (*Photomicro: Dr. J. Bell.*)

The plague bacillus (Fig. 39), as seen in a blood-film, or in preparations from any of the other tissues, is a short, thick, cocco-bacillus (1·5 to 2 by 0·5 to 0·7 μ) with rounded ends, very like the bacillus of chicken cholera. A capsule, or the appearance of one, can generally be made out, especially in bacilli in the blood. The organism is readily stained by aniline dyes, especially by Romanowsky stains, the extremities taking on a deeper colour than the interpolar part, giving it a bipolar appearance. It is usually decolorized by Gram. Epstein regards the bipolarity as a phenomenon not specially confined to *B. pestis*; the fixing and staining of the specimen naturally influence the result.

Culture characters.—When sown on blood-serum and kept at body-temperature, in from twenty-four to forty-eight hours an abundant moist, yellowish-grey growth is formed without liquefaction of the culture medium. On agar, but better on glycerin-agar, the growths have a greyish-white appearance. In agar plate cultures they show a bluish translucence, the

individual colonies being circular, with slightly irregular contours and a moist surface; on mannite-neutral-red-bile-salt agar the colonies are bright red, but are colourless on a similar medium in which lactose is substituted for mannite. Litmus-milk and glucose-broth are rendered slightly acid; lactose-broth is unchanged. Young colonies are glass-like, but older ones are thick at the centre and more opaque; they are singularly coherent and may be removed *en bloc* with a platinum needle. Stab-cultures show after one or two days a fine dust-like line of growth. According to Yersin, when sown on gelatin the bacillus gives rise to white transparent colonies which, when examined in reflected light, present iridescent borders. In bouillon the cultures present a characteristic appearance: the liquid remains clear,

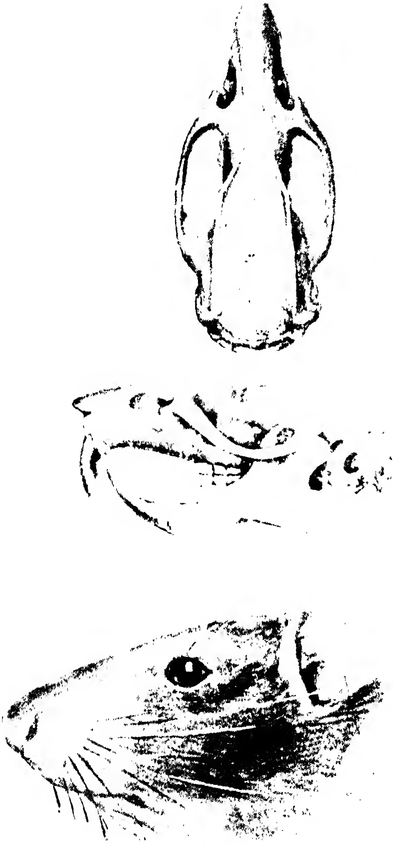


Fig. 40.—*Rattus norvegicus.*

Configuration and anatomical characters of head and skull (nat. size).

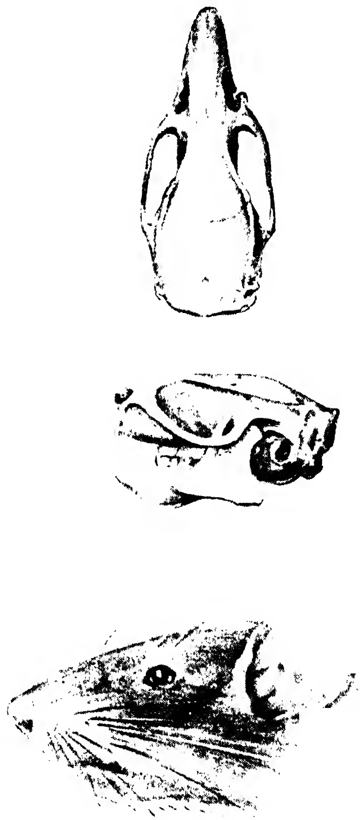


Fig. 41.—*Rattus rattus.*

Configuration and anatomical characters head and skull (nat. size).

whilst a granular deposit takes place on the sides and bottom of the tube. Cultivated on broth in which clarified butter or coco-nut oil is floated, *B. pestis* presents characteristic stalactite growths which gradually fall off, forming a granular deposit. Examined with the microscope, these various cultures show chains of a short bacillus, presenting here and there large bulbous swellings. In gelatin the bacilli sometimes form fine threads, sometimes thick bundles made up of many laterally-agglomerated bacteria, and involution forms are common. The bacillus does not produce spores.

The most favourable temperature for culture is from 36° to 39° C.

The virus of plague can be modified by artificial methods; it is well known that some process of this kind takes place in nature, for as a plague epidemic decreases, so the case-mortality falls.

Experimental plague.—In the case of the guinea-pig, within a few hours of the introduction of the virus a considerable amount of œdema is already apparent around the puncture, and the adjacent gland is perceptibly swollen. At the end of twenty-four hours the animal is very ill; its coat is rough and staring, and it refuses food, and presently becomes convulsed. If the body is opened immediately after death, a sanguineous œdema is found at the point of inoculation, with hæmorrhagic inflammatory effusions around the nearest lymphatic gland, which is much swollen and full of bacilli. The intestines are hyperæmic; the adrenals, kidneys, and liver are red and swollen. The much-enlarged spleen frequently presents an eruption of small whitish granulations resembling in appearance miliary tubercles. All the organs, and even any serous fluid that may be present in peritoneum or pleura, will be found to contain plague bacilli. In the blood, besides those free in the liquor sanguinis, bacilli are to be found in the mononuclear, though not, it is said, in the polymorphonuclear leucocytes.

Rôle of the rat in plague.—Although small and circumscribed epidemics of plague may occur without the intervention of the rat, as when it first appeared in Colombo, there can be no doubt that in most epidemics of the bubonic form this rodent plays an important part both in the introduction and in the spread of infection. The species principally concerned are *Rattus norvegicus* (or *decumanus*), the grey rat, and *Rattus rattus*, the black rat (Figs. 40, 41). The mouse, *Mus musculus*, is also susceptible. The bandicoot and musk-rat are of little importance in these respects, although susceptible to the infection. In Bombay the epizootic appears first in the *Rattus norvegicus* community, *Rattus rattus*—the more domestic species—being subsequently attacked. Later the disease appears in epidemic form in man (Chart 13).

The seasonal prevalence of bubonic plague in rats is marked, and is not due to a periodicity in their reproduction, but is connected with periods in which fleas are most numerous.

In places in which plague epidemics keep recurring year after year, the local rats acquire a considerable degree of immunity; moreover, this immunity is transmitted hereditarily. Thus, in plague-free towns in India—e.g. Madras and Dacca—the mortality among the local black rats experimentally infected was 100 per cent., while in plague-stricken towns, such as Cawnpore and Poona, it was much less.

Another observation, already referred to, which together with the foregoing may have important bearings on the spread of plague and the yearly recurrence of epidemics in the same place, is that in certain rats the disease may assume a chronic form.

Rats have been known to quit villages in anticipation of the advent of the disease.

Other animals may die of plague during an epidemic ; oxen, sheep, deer, pigs, may all be attacked at times. Dogs are immune.

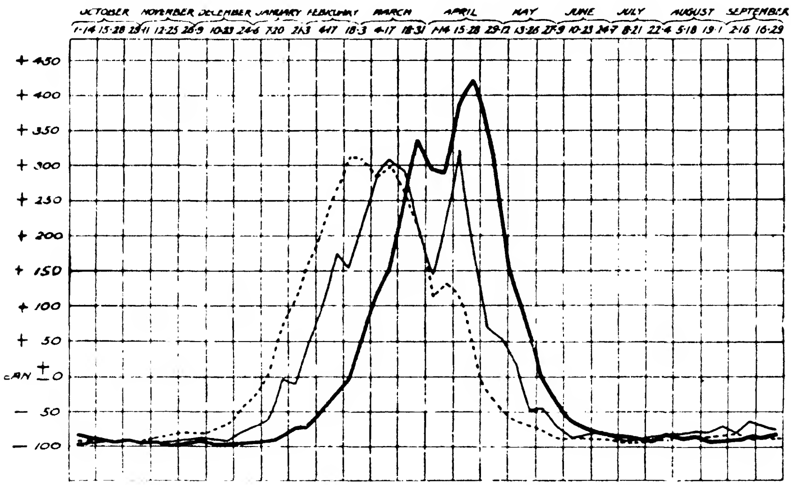


Chart 13. Showing progress of plague in rats and man.
(" *Report of Indian Plague Commission.*")

········ Infected *R. norvegicus.*
Infected *R. rattus.*
———— Human deaths from plague.

Rôle of the marmot and other rodents.—Mongolian and Siberian pneumonic plague epidemics are associated with the occurrence of the disease in species of marmot known as " tarabagan " (*Arctomys bobac*, Fig. 42),[1] and several smaller species (*Citellus citellus* and *C. mugozaricus*), locally known as " susliks," which can harbour the plague bacillus in their bodies without apparently suffering any ill effects during hibernation, thus constituting a more or less permanent reservoir of the plague virus. Possibly the plague infection is transmitted to man by the fleas which infest these animals, but it is more generally considered that the rodent fleas play a minor part and that the infection is transmissible *via* the alimentary tract. It has been shown that in hibernating spermophiles *B. pestis* loses its

[1] A subspecies of *A. bobac, Arctomys centralis,* was found infected in the Narinsk epidemic of 1929-30.

virulence and is less easily cultivated. Epizootics of plague in these regions generally begin after hibernation.

The pouched marmot of the Caucasus (*Spermophilus guttatus*) is extremely susceptible to plague infection, and is probably concerned in the spread of the disease in that region. In Transbaikalia plague occurs in *Spermophilus eversmani* and in *S. dauricus*. The latter animal is 22 cm. long and rather resembles the tarabagan. It is said that its presence can be determined by the appearance of characteristic excrement at the mouth of the burrows.

Fig. 42.—*Arctomys bobac*, **Siberian marmot** (nat. size).

Fig. 43.—*Citellus beecheyi*, **ground-squirrel of California** (nat. size).

As an indication of the important part that many animals play in the spread of human plague, extracts from the report of the first Plague Congress of Soviet Russia, 1927, may be taken as an example. In South-East Russia, from October, 1925, to May, 1927, there were 42 plague epidemics with 310 cases. The infection of 11 of these originated from domestic and field mice, four from spermophiles, three from jerboas (*Dipodipus sagita*), and four from gerbilles (*Rhombomys opimus*), while seven outbreaks were traced to infection at slaughter of plague-infected camels. Fleas capable of biting man were found on nearly every rodent, and play an active part in the spread of plague in Russia. Proventricular blocking (*see* p. 285) with the plague bacillus occurs in the gerbille fleas (*Ceratophyllus tesquorum* and *C. lævïceps*).

Plague is known to exist in the seven western states of America, but it has not so far been noted east of Wyoming nor south of Utah, save in California; the most northerly point is some 150 miles north of the Californian border. In California the ground-squirrel (*Citellus beecheyi*, Fig. 43), although it does not live near human habitations, infects rats that do, and thereby acts as an important reservoir of *B. pestis*.

Seven species of ground-squirrels are now known to harbour plague, including *Citellus beecheyi*, *C. grammurus*, and *C. townsendi*. Other wild rodents from which plague-infected fleas have been collected include a tree-squirrel (*Sciurus douglasii*), chipmunks (*Eutamias sp.*), marmots (*Marmota flavirenter nosophora* and *M. fl. engelhardti*), and also prairie dogs (*Cynomys parvidens*). The last have only recently been proved to be plague rodents.

In South Africa, especially in the Cape Province, different conditions reign, for there it has been found that the rodents of the inland veld have become infected with plague, and by continuously passing the disease from one to another constitute a persistent and dangerous source of human infection. On the high veld the gerbilles (*Taterona lobengula* and *Desmodillus auricularis*), the ground-squirrel (*Geosciurus capensis*), and the multimammate mouse (*Mastomys coucha*) are the most important—the latter forming a link by conveying infected fleas from gerbille burrows into human habitations. In the lower bush country the striped mouse (*Rhabdomys pumilio*) plays the chief rôle, while the springhaas (*Pedetes caffer*), a giant jerboa, on account of its extreme mobility is capable of widely disseminating plague. Two carnivores, the suricate and the yellow mongoose are susceptible to plague by feeding on dead and dying rodents, and it has been pointed out by Mitchell that the discovery of gerbille remains in the fæces of these animals is a valuable indication of the existence of a rodent epizoötic in the veld districts, as these animals do not normally eat gerbilles unless they are sick.

South African rodents harbour a large number of species of fleas. Of these, three, *Dinopsyllus lypusus*, *Chiatopsylla rossi* and *Xenopsylla eridos* have been found, under experimental conditions, capable of conveying plague infection.

To be effective, the prophylaxis of plague in the wilder regions of the world necessarily entails a knowledge of the habits of these rodents. The ground-squirrels are really spermophiles which constitute a connecting link between the true squirrels and the marmots. Ground-squirrels are generally to be found in prairie-like regions, where they form an intricate system of burrows, at the main entrance of which they may be commonly seen standing on guard upright and motionless.

The true marmots, such as the "tarabagan," are characterized by the rudimentary character of the thumb, and their small eyes and ears; the tail is bushy and comparatively short. The burrows which they excavate are very deep and are crowned by mounds of earth thrown up by successive

generations of marmots and are known as "bootans" in Mongolia. The gerbilles are small jerboas; they are rather smaller than the domestic black rat; the hind legs are long, the front very short. In colour they are pale fawn with white bellies. Their habitat is sandy country where they live in families. Their warrens extend over an area of 30 square yards and to a depth of 3–4 feet. Gerbilles may commonly be seen sitting warily in an upright position at the mouth of their burrows with front paws extended horizontally. The warrens often harbour ground-squirrels, suricates and mongooses, all four species, apparently, living on friendly terms. It has been shown that plague is spread among gerbilles (*Taterona lobengulæ*) through the intestinal tract by the cannibalistic habits which these creatures develop when sick.

The multimammate mouse is the wild mouse of the veld and has much the same habits; in country districts it invades human habitations. The striped mouse is diurnal in habit and is more numerous in bushy country, where it usually builds big nests of sticks on the surface of the ground and lives in large families.

In Dakar (Senegal) a shrew (*Crocidura stampflii*) plays a part in the dissemination of the disease. On the Gold Coast, the giant rat (*Cricetomys gambianus*), and in Kenya the field rat (*Arvicanthus abyssinicus*) are important.

In South America, in the Argentine pampas, Uriarte and Villażon have shown on several occasions that rodents of the cavy type suffer in plague epizoötics. The species specially concerned are *Microcavia australis* and *M. galea*; a cricelid also, *Graomys griseoflavus*, has been shown to be experimentally very susceptible. It is arboreal in its habits and recently de la Barrera has found a small outbreak of human plague which was traced to this animal.

On observations such as these the modern quarantine against plague has been framed.

Rôle of the flea in plague.—It is now known that plague is not communicable from animal to animal by simple contact, but is readily communicated by fleas, and principally by *Xenopsylla cheopis* (Fig. 352, p. 1018), the rat-flea of the tropics; *Ceratophyllus fasciatus*, the rat-flea of temperate climates; and *Ctenocephalus canis* and *C. felis*, which bite men, dogs, and rats indifferently; these act as passive intermediaries and carriers of the bacillus. *B. pestis* multiplies in the stomach of the flea, retaining its virulence for over twenty days, and is then passed out in the fæces; so that the flea serves not only as a carrier, but also as a multiplier of the germs. Wu Lien Teh has shown that in outbreaks of plague in Manchuria the human flea (*Pulex irritans*) may convey the bacillus direct from patient to patient without the intervention of the rat.

Especially convincing are the experiments of the Indian Plague Commission, which clearly showed that, if fleas are excluded, healthy rats will not contract the disease, even if kept in intimate association with plague-infected rats. Young rats may even be suckled by their plague-stricken mothers and remain healthy. It suffices to transfer

fleas from a plague animal on to a healthy animal, or to place the latter in a room in which plague rats have died recently and been subsequently removed. The fleas that have left the body of the dead rats, remaining in the room, convey the bacillus. An animal placed on the floor cannot be infected if the precaution is taken to surround the cage with "tangle foot," so as to keep off the fleas; but if it be placed on the unguarded floor, either in its cage or allowed to run about, or even if suspended 2 in. above the floor—a distance not beyond the saltatory powers of the flea—it will become infected.

Martin and Bacot found that a proportion of the fleas fed on plague-infected rats develop a peculiar condition of stomach and œsophagus,

Fig. 44.—*a*, **Flea viewed as a transparent object; the proventriculus and stomach contain a mass of plague-culture.** *b*, **Flea's stomach, obstructed by growth of plague-culture.**

Œs., Distended œsophagus containing fresh blood; P.C., obstructing mass of plague-culture.

This figure illustrates the method of transmission of *B. pestis* by *Ceratophyllus fasciatus*.

(*By permission of Sir C. J. Martin, "Journ. of Hyg.," 3rd Plague Suppl., Jan.*, 1914.)

these organs becoming blocked with blood-clot containing a pure culture of *B. pestis*. When such a flea feeds on a normal rat, part of the culture regurgitates and communicates infection; at the same time bacilli are passed in the fæces and may infect through any existing abrasion. They further observed that the "blocked" fleas died very rapidly, apparently of thirst, if placed in a warm, dry atmosphere (Fig. 44).

In temperate climates fleas are most numerous during the warmer seasons of the year; hence summer and autumn is the bubonic plague season in such climates. In warm climates bubonic plague is most prone to become epidemic at those times of the year when temperature ranges between 10° and 30° C.—temperatures favourable to the multiplication and activity of the flea. Temperatures over 30° C.

are unfavourable to it, especially if the atmosphere is dry. Pneumonic plague, not being spread by this insect, is not influenced by temperature in this way.

The flea, then, communicates plague either by its fouled mandibles, by regurgitation in the act of sucking, or by provoking scratching and consequent inoculation of the bacilli deposited in its fæces.

The capacity of a flea's stomach is about $\frac{1}{2}$ c.mm., and in most cases of human bubonic plague there are not sufficient plague bacilli in the peripheral blood-stream to infect it with any regularity, except in the terminal stages of fatal cases. The human flea, *Pulex irritans*, which occurs in enormous numbers, especially in Morocco, may become infected; but there is no convincing evidence to show that it ever plays a dominant part.

It has long been known that large tracts of country and important cities in India, such as Madras, have remained immune from plague, though in constant communication with plague-infected centres. In 1914 Rothschild and Jordan pointed out that the rat-fleas of Indian cities belonged to three closely allied species—*X. cheopis*, *braziliensis*, and *astia*—and soon afterwards Hirst and Cragg pointed out that in those districts in which plague was uncommon *X. astia* replaced *cheopis* as the common ectoparasite of the rat. From this and other experimental evidence it is now assumed that this species is unable to convey the plague infection in the same manner as *X. cheopis* (*see* p. 1018).

Bionomics of the rat-flea.—In ordinary circumstances the rat-flea completes its developmental cycle in from fourteen days to three weeks, but in warm damp weather this may be shortened to ten days. The average life of a flea, separated from its host, is about ten days, but it is capable of remaining alive without food for two months, should the temperature of the air be low at the time. In tropical temperatures the insect can harbour the plague bacillus without feeding on blood for forty-five days.

Apart from the very serious danger arising from vermin affected with chronic plague, which may hang about a house for a long time, it would appear that the house itself does not retain the infection for any length of time. The Plague Commission has shown that floors of cow-dung contaminated with *Bacillus pestis* do not remain infective for more than forty-eight hours, and that floors of "chunam" cease to be so in twenty-four hours.

Evidence of rat-mortality is not always conspicuous even when the epizoötic is severe. No *dead* rats may be found in the open, but many if search is made in the right situations. In Madagascar it has been shown that rat-fleas (*X. cheopis*) may survive in dust and spread infection long after the bodies of the defunct rats have disappeared.

Pathology.—After death from plague the surface of the body very frequently presents numerous ecchymotic spots or patches. The number and extent of these vary, apparently, in different epidemics. In some epidemics

the cutaneous hæmorrhages have been both extensive and numerous.[1] The characteristic buboes are generally apparent; occasionally there are also furuncles, pustules, and abscesses. Rigor mortis is usually moderate; sometimes post-mortem muscular contractions, like those in cholera, take place. Post-mortem rise of temperature is often observed. Decomposition is said to set in early.

The characteristic appearance of plague in a necropsy is that of engorgement and hæmorrhage, nearly every organ of the body participating more or less. There is also parenchymatous degeneration in most of the organs. The brain, spinal cord, and their meninges are markedly congested, and there may be an increase of subarachnoid and ventricular fluid. There are numerous and pronounced puncta cruenta on the brain sections; occasionally there may be considerable extravasations of blood into the substance of the brain (mesencephalon and medulla oblongata).

Ecchymoses are common in all serous surfaces; the contents of the different serous cavities may be sanguineous. Extensive hæmorrhages are occasionally found in the peritoneum, mediastinum, trachea, bowel, stomach, pelvis of kidney, ureter, bladder, or in the pleural cavities. The lung frequently shows evidences of bronchitis and hypostatic pneumonia; sometimes hæmorrhagic infarcts and abscesses are found. The right side of the heart and the great veins are usually distended with feebly coagulated or fluid blood. In pneumonic plague the superficial lymphatic glands are not enlarged; the pleural cavities contain blood-stained serum; the infected lungs are deeply congested and œdematous, and at a later stage pneumonic consolidation is found. The bronchi contain blood-stained serum, and the bronchial glands are swollen and hæmorrhagic.

The liver is congested and swollen and its cells are degenerated. The spleen is enlarged to two or three times its normal size. The kidneys are in a similar condition. The mucosa of the alimentary canal as a whole is congested, showing here and there punctate ecchymotic effusions and, occasionally, hæmorrhagic erosions, and even—especially about the ileo-cæcal valve—ulcerations.

Evidence is invariably discoverable of serious implication of the lymphatic system; around the glands there is much exudation and hæmorrhagic effusion, with hyperplasia of the gland-cells, and an enormous multiplication of bacteria.

Symptoms. *Incubation period.*—Symptoms of plague begin to show themselves after an incubation period of from two to eight, rarely fifteen, days.

The average case of plague: prodromal stage.—In a certain but small proportion of cases there is a prodromal stage characterized by physical and mental depression, anorexia, aching of the limbs, feelings of chilliness, giddiness, palpitations, and sometimes dull pains in the groin at the seat of the future bubo.

Stage of invasion.—Usually, the disease sets in somewhat suddenly with fever, extreme lassitude, frontal or, more rarely, occipital headache, aching of the limbs, vertigo, drowsiness or perhaps

[1] It has been pointed out by MacArthur that the term "Black Death" (*Pestis atra*) did not refer to these hæmorrhages, but to the terrible nature of the disease.

wakefulness, or troubled dreams. Rigor is rarely a marked feature; more often the disease is heralded by feelings of chilliness. The face quickly acquires a peculiar expression, the features being drawn and haggard, the eyes bloodshot, sunken and staring, the pupils probably dilated; sometimes the face wears an expression of fear or horror. The patient, if he can walk, drags himself about in a dreamy sort of way, or he staggers like a drunken man. There may be nausea and vomiting: in some instances there is diarrhœa.

Pestis minor, or ambulatory plague.—Abortive or ambulatory cases of true bubonic plague have been reported recently in connection with almost every true outbreak of the disease. Joltrain reported several of these cases in connection with the Paris outbreak of 1920 and also in Algeria; Leger has described similar cases in Dakar, and Fonquernie in Madagascar. Clinically these cases present mild, general febrile symptoms with a bubo, and when that suppurates the temperature falls and the patient recovers. The diagnosis may be difficult because the plague bacillus may be very scanty in the pus. The differential diagnosis has, of course, to be made from climatic bubo (*Lympho-granuloma inguinale*).

Stage of fever.—The stage of invasion may last for a day or two without a serious rise of temperature occurring. Usually it is of much shorter duration; or it may be altogether wanting, the disease developing abruptly without definite rigor or other warning, the thermometer rising rapidly to 103° or 104°, or even to 107° F., with a corresponding acceleration of pulse and respiration. The skin is now dry and burning, the face is bloated, the eyes are still more injected, sunken and fixed, the hearing is dulled. The tongue is swollen and covered with a creamy fur, which rapidly dries and becomes brown or almost black; sordes form on the teeth and about the lips and nostrils. Thirst is intense, prostration extreme, the patient from utter weakness being hardly able to make himself heard. Sometimes he becomes delirious; the delirium may be wildly furious, or fatuous, or of a low muttering type. Coma, convulsions—sometimes of a tetanic character—retention of urine, subsultus tendinum, and other nervous phenomena may occur. Vomiting is in certain cases very frequent. Some patients are constipated, others have diarrhœa. The spleen and liver are usually both enlarged. Urine is scanty, but rarely contains more than a trace of albumin. The pulse, at first full and bounding, in the majority of cases rapidly loses tone, becoming small, frequent, fluttering, dicrotic, intermittent. In the later stages the heart may be dilated, the first sound being feeble or absent.

Bubonic plague.—In about three-fourths of the cases, some time between the first few hours and the fifth day, generally within twenty-four hours, the characteristic bubo or buboes develop. Usually (in 70 per cent.) the bubo forms in the groin, most frequently on the right side, affecting one or more of the femoral glands; less frequently (20 per cent.) in the axillary glands; and still more rarely (10 per

cent.), and most commonly in children, those at the angle of the lower jaw are affected. In rare cases the tonsil may be the source of infection and cervical buboes may actually result. The buboes are usually single; in about one-eighth of the cases, however, they form simultaneously on both sides of the body. Very rarely are buboes formed in the popliteal or in the epitrochlear glands, or in those at the root of the neck. Occasionally buboes occur simultaneously in different parts of the body. It is a curious fact that in squirrel-conveyed plague the buboes almost invariably occur in the axilla.

The buboes vary considerably in size. In some instances they are not as large as a walnut; in others they attain the size of a goose's egg. Pain is often very severe; on the other hand, it is sometimes hardly complained of. Besides the enlargement of the gland, there is in most instances distinct infiltration of the surrounding connective tissue.

In a very small proportion of cases what are usually described as carbuncles, which are in reality small patches of moist gangrenous skin that may gradually involve a large area, develop on different parts of the integument. These occur either in the early stage or late in the disease. Sometimes they slough and lead to extensive gangrene.

Kirk and Crawford have described a generalized eruption which takes the form of a papular rash on the hands, feet and pectoral region. Should life be continued sufficiently long, the vesicles become converted into pustules. These observations confirm in a remarkable manner, as MacArthur has pointed out, those of the old writers in describing manifestations known in the Plague of London of 1665, as "blains."

In favourable cases, sooner or later, after or without the appearance of the bubo, the constitutional symptoms abate with the setting in of profuse perspiration. The tongue now begins to moisten, the pulse-rate and temperature to fall, and the mild delirium, if it has been present, to abate. The bubo, however, continues to enlarge and to soften. After a few days, if not incised, it bursts and discharges pus and sloughs—sometimes very ill-smelling. In rare instances suppuration is delayed for weeks; whilst in some the bubo subsides after a few weeks, or perhaps months, without having broken down. Convalescence, when it occurs, sets in some time between the sixth and tenth day, although it may be delayed for a fortnight or three weeks. Occasionally a pyæmic condition, with boils, abscesses, cellulitis, parotitis, or secondary adenitis, succeeds the primary fever. It is reported that plague bacilli can be cultivated from buboes 66 days after the patient has become ill, and in fact the first bacteriological examination may be negative. The sores left by the buboes and abscesses of plague are extremely indolent and may take months to heal. Secondary pneumonic plague with blood-stained sputum may supervene from which the patient may recover.

Hæmorrhages of different kinds are not an unusual feature of plague—ecchymotic effusions of a purplish or dull-red tint, and varying in size from a hemp-seed to spots half an inch in diameter. These hæmorrhages are found frequently in certain malignant epidemics of plague.

Abortion almost invariably occurs in pregnant women ; the fœtus sometimes shows signs of the disease.

Death may take place at any time in the course of plague. Usually it occurs between the third and fifth day, with symptoms of profound adynamia, heart-failure, or perhaps from convulsions, from coma, from internal hæmorrhage, or, later, from exhaustion consequent upon prolonged fever or suppuration, or from secondary hæmorrhages.

Certain epidemics are distinguished by the large proportion of mild cases, the so-called *pestis minor*.

Septicæmic plague, or pestis siderans.—In this type there is no special enlargement of the lymphatic glands apparent during life, although after death the glands throughout the body are found to be somewhat enlarged and congested. The high degree of virulence and the rapid course of the disease depend on the entry of large numbers of the bacilli into the blood, where they can be readily found during life. The patient is prostrated from the outset ; he is pale and apathetic ; there is generally little febrile reaction (100° F.). Great weakness, delirium, picking of the bed-clothes, stupor, and coma end in death on the first, second, or third day, or, it may be, later. Frequently in these cases there are hæmorrhages.

Pneumonic plague occurs frequently among the marmot-trappers of Northern China, who live under very insanitary conditions. It is especially dangerous to the patients, attendants, and visitors, because of the multitude of bacilli which are scattered about in the patient's expectoration, and because the clinical symptoms are unlike those of typical plague and are apt to be mistaken for some ordinary form of lung disease. The illness commences with rigor, malaise, intense headache, vomiting, general pains, fever, and intense prostration. Cough and dyspnœa set in, accompanied by a profuse, watery, blood-tinged sputum. The sputum is not viscid and rusty, as in ordinary pneumonia. From the commencement the clouding of consciousness is very marked. Moist râles are audible at the bases of the lungs, the breathing becomes hurried, other symptoms rapidly become worse, delirium sets in, and the patient usually dies on the fourth or fifth day. This is the most fatal as well as the most directly infectious form of plague. Epidemics of 50,000 and more cases have occurred in Manchuria, where the plague bacillus exists as an intestinal infection in the marmot, which acts as a reservoir of the virus. Pneumonic plague has been recorded from Nigeria and the Gold Coast. It has been found that in these countries hæmorrhage into the intestinal canal occurs in about 8 per cent. of plague-infected rats and the organism is passed

out in the fæces; in this manner the plague bacillus can be disseminated in dust and inspired by man directly into the lungs. (Connal and Paisley.)

Relapses of all forms of plague, though rare, do occur, and are dangerous. It has been pointed out by Kellog that, whereas in rat-borne plague pneumonia is rare, in squirrel plague it is the reverse.

Meningeal plague.—Meyer and his colleagues have described a chronic relapsing meningeal form of plague in California, in which the patients exhibit meningeal symptoms with high fever. The plague bacillus can be isolated from the blood.

Mortality.—The case-mortality of bubonic plague varies in different epidemics. It is usually greatest at the beginning and height of the epidemic. The death-rate may be anything from 60 to 95 per cent. of those attacked. Much appears to depend on the social condition of the patient and the attention and nursing available. Thus in a Hong Kong epidemic, while the case-mortality among the indifferently fed, overcrowded, unwashed, and almost unnursed Chinese amounted to 93·4 per cent., it was only 77 per cent. among the Indians, 60 per cent. among the Japanese, and 18·2 per cent. among the Europeans—a gradation in general correspondence with the social and hygienic conditions of these different nationalities. In the South American epidemics and in the recent circumscribed epidemics in Europe the mortality was only about one-third of that obtaining in India and China. Pneumonic plague is generally fatal in from three to four days. Van den Berg and Vos report that in an epidemic in Java (1930) in 66 cases of plague the mortality was 76 per cent. The sixteen who recovered had all been suffering from bubonic plague. The chances of recovery were somewhat better in men than in women. In this series there were 57 cases of bubonic plague, two of plague ulcers, 29 of septicæmic plague, and one of primary plague pneumonia.

Diagnosis.—The occurrence of fever and adenitis during a plague epidemic must invariably be viewed with suspicion, and particularly if the fever rapidly assumes an adynamic character. In the early stages diagnosis may be very doubtful, especially in pneumonic plague, and in the countries of high filarial endemicity and in which filarial adenitis is necessarily a common occurrence. Blood-culture is recommended by Onoto by inoculating blood into broth containing 1 per cent. of sodium citrate. Rosier states that in Java splenic puncture constitutes a valuable procedure in establishing a diagnosis and is not opposed by the native population. In Western America the differentiation of mild cases of plague from tularæmia is important (p. 302). The discovery of the bacillus in the glands, blood, sputum, or discharges is the only thoroughly reliable test, while there is an associated leucocytosis. Should a cocco-bacillus be found with the characteristic bipolar staining, it should be cultivated by Haffkine's method in broth on which clarified butter (ghee) or coco-nut oil is floated (*see* p. 278). In case of doubt, animal inoculation should be

resorted to ; a little of the virus from the patient or a culture is rubbed into a shaven area (1 in. square) on the abdomen of a white rat or a guinea-pig. *B. pestis* inoculated in this way kills the guinea-pig in seven days, the rat sooner, and white mice in forty-eight hours. The latter may be inoculated at the root of the tail.[1]

B. pestis and *B. pseudotuberculosis rodentium* (the cause of a distinct disease in rodents) closely resemble each other and are scarcely distinguishable by the usual cultural methods. There is no detectable difference between them ; neither coagulates milk, but in agar the former produces a more glistening membranous growth. *B. pseudotuberculosis rodentium*, however, produces a clear, yellowish growth on potato. On Drigalski medium it is said to produce blue colonies, and *B. pestis* reddish ones. The former also readily associates itself with the production of smooth and rough colonies with all degree of transitions between them. The smooth colonies show closest association to *B. pestis* and are the most virulent.

The most satisfactory means of differentiation is animal inoculation. Rabbits, guinea-pigs, and white mice are susceptible to *B. pseudotuberculosis*, but white rats are not. The Indian Plague Commission laid stress on the latter point, as these animals are instantly killed by *B. pestis*.

Differential diagnosis.—Bubonic plague has sometimes to be distinguished from other affections associated with enlarged glands, such as streptococcal infections, *lymphogranuloma inguinale* and filarial adenitis, and occasionally from an anthrax pustule.

In filarial and streptococcal infections lymphangitis tracks are usually visible, but in bubonic plague there is usually no visible sign of the primary infection. In glandular fever the cervical glands are as a rule primarily affected and there is an excess of heterophil antibodies in the serum (goat's corpuscle test).

Generalized pustular plague has to be differentiated from chicken-pox or smallpox ; carbuncular plague may be mistaken for anthrax ; and septicæmic plague may be confused with typhus. In the United States, North Europe and Russia, tularæmia may resemble plague very closely indeed.

Pneumonic plague differs from other forms of pneumonia in three main characteristics : (1) The patient is extremely prostrate, although his critical state can hardly be accounted for by such physical signs as are present in the chest ; but by the time definite involvement of the lung can be demonstrated, he generally dies. (2) The sputum is watery, never thick, and soon becomes very blood-stained. (3) Pleural effusion is usually present in plague pneumonia.

[1] *Post-mortem indications of plague in the rat.*—Before rats suspected of being plague-infected are handled, they should be immersed in disinfectant to destroy ectoparasites.

The lymphatic glands should be first exposed. If the rat is infected, subcutaneous injection around the glands is generally recognizable. If the gland is itself inflamed, this is almost diagnostic of plague ; in which case the liver will be of a yellow colour and sprinkled with innumerable pinky-white granules. The spleen is enlarged, congested, and occasionally granular. Serous or blood-stained serous effusions are present in 72 per cent. of such rats ; if, on microscopical examination of scrapings from glands or spleen, bipolar-staining bacilli are detected, the case is probably plague. Too great stress must not be laid on bipolar staining alone, as this feature depends somewhat on the method of staining ; it is best demonstrated by the Leishman eosinazur stain.

Treatment.—The treatment of plague is mainly symptomatic. The asthenic tendencies of the disease must ever be borne in mind, and depressant remedies of all kinds carefully avoided.

During the earlier stages, when headache and perhaps high fever are urgent, much relief may be obtained from ice-bags to the head and neck. If it be deemed advisable to attempt to lower the temperature, sponging of the body every hour with warm water is a much safer measure than the employment of antipyrin and similar drugs. Vomiting is usually relieved by a full dose of calomel followed by a saline. If not, or if diarrhœa be present, Lowson recommended ice pills and an effervescing mixture containing morphia and hydrocyanic acid. Sinapisms to the epigastrium are useful. In collapse, stimulants of various kinds, including strong ammonia to the nostrils, and ether hypodermically, are indicated; they sometimes succeed in resuscitating a sinking patient. Given with judgment, morphia is by far the best hypnotic. Hyoscine ($\frac{1}{200}$ to $\frac{1}{75}$ gr.) or chloral (20 gr.) and bromide of potassium (30 gr.) are of service for the same purpose. Diarrhœa, if urgent, is best treated by intestinal antiseptics, as salol in 10-gr. doses every four hours. The buboes in the early stage may be treated with applications of glycerin and belladonna. Should they become red and inflamed, they must be poulticed and, on softening occurring, incised and dressed with iodoform. Indolent bubonic swellings should be treated with iodine liniment. Feeding and stimulation are to be conducted on ordinary principles. The injection directly into the buboes of iodine and a solution of camphor and thymol mixed in equal parts, in doses of $\frac{1}{2}$ to 1 c.c., according to the age of the patient, has been advocated. Intravenous injections of iodine have gained a certain reputation. A 1-per-cent. solution with double the amount of potassium iodide is injected in doses of 5 to 10 c.c. daily for four days.

Serum-therapy.—Yersin, Calmette, and Borrel immunized a horse by intravenous injections of living virulent cultures and produced an effective antiserum. It must be given intravenously in large doses (100–250 c.c.), and frequently repeated. The injections, in order to be effective, must be made early in the course of the disease. More recently the effect of an anti-plague serum has been tried out in India, and Dawson reports that in bubonic plague, in doses of 30–40 c.c., the results have been more encouraging. Robic has given plague serum intravenously in plague pneumonia. E.V., an avirulent strain of *B. pestis*, is used for producing the serum.

Mercurochrome 220 soluble (dibromo-oxy-mercury-fluorescein).—The success attending the intravenous injection of this drug in various septicæmic states led to the hope that it would prove of use in septicæmic plague. The drug is given in a 1-per-cent. solution in water and the tolerated dose is 2 to 5 mg. per kilo of body-weight. It has been given to a few cases of plague with encouraging results. The dose is 20 c.c. of a 1-per-cent. solution, an amount which can be

increased in subsequent injections. In Java a substance called Omnadin, in 2 c.c. doses, has been injected in cases of pneumonic plague.

Sulphanilamides.—Schütze (1939) has tested the efficiency of these preparations, especially M & B 693, against plague infection in rats and mice. The drugs were given by the mouth and subcutaneously. M & B 693 proved to be most efficacious, and had also a slight protective value. Given subcutaneously the sulphanilamide gave results comparable to that of Otten's antiplague serum.

Carman has reported encouraging results in the treatment of human plague with prontosil soluble *rubrum.* The injections were made intramuscularly twice daily in doses of 2·5–5 c.c.

Bacteriophage (*Pestifage*).—Bacteriophage substances are regarded by d'Herelle as separate self-multiplying particulate organisms preying upon bacterial cells. Others, like Bordet, regard them as the products of a chemical perversion arising in the bacterial cell. On the lines laid down by d'Herelle, a potent antiphage serum has been prepared in India, but the therapeutic results so far obtained have been distinctly disappointing. In bubonic plague the phage is administered subcutaneously into the bubo in doses of 2–3 c.c. on the first, and again on the second days. In septicæmic plague 3 c.c. or more have been given intravenously. Couvy and his co-workers report upon 21 severe cases of bubonic plague with 15 recoveries, and a preliminary densensitization by subcutaneous injection of the patient's own blood (autoæmotherapy) is recommended.

General prophylaxis.—The prophylaxis of plague, as of other infectious diseases, has to be considered from the standpoint of the community and also from that of the individual. As regards the former, it includes measures for preventing the introduction of the virus, for staying its spread if introduced, and for securing its destruction.

Quarantine.—Modern systems of land or sea quarantine directed against plague take cognizance of the facts that the incubation period of the disease may extend to ten days, and that plague affects certain of the lower animals as well as man. Ten days is the minimum period that should elapse between the time of departure from an infected place, between the date of the last death, or between the arrival of a ship or batch of travellers with cases of plague in progress among them, and the granting of free pratique. Moreover, as Kitasato has shown that the specific bacillus persists in the bodies of those who have recovered from plague for at least three weeks from the cessation of the active disease, convalescents should be isolated for a month before they are allowed to mingle with an uninfected community.

In ships coming from an infected port the rats, mice, and similar vermin should be destroyed, thrown overboard and sunk before harbour is entered. The generation of sulphurous-acid gas under pressure, especially by the Clayton system, has been found useful for their destruction.

The most suitable and practicable disinfectants are steam,

1 : 1000 corrosive sublimate in carbol-sulphuric acid, lysol, chloride of lime in 1-per-cent. solution, carbolic acid 5-per-cent., and formalin 2-per-cent.

On plague breaking out in a small village community, as soon as the disease is recognized, measures should be taken to prevent the inhabitants leaving the locality and thus disseminating it. There is little danger of this until the inhabitants become alarmed by a rapid extension of the disease. If possible, after the patients have been isolated in a special hospital, the village should be evacuated for a month. The safest and most thorough form of disinfection is by fire, and in the case of an isolated village prompt destruction of the infected houses by this means is the surest method of stamping out the infection. The clothes and bedding of all patients should be burned. The dead should, with as little delay as possible, be buried in deep graves or cremated. Isolated observation camps should be organized, in which "suspects" and "contacts" may be segregated for a time equal at least to the incubation period of the disease. War should be waged against all rats and mice, and their corpses burned.

In the event of an outbreak in a town, it must be borne in mind that plague, once established in human beings, is communicable to others and to rats by means of the expectoration, by the discharges from the bowels, by the urine, and by discharges from the buboes or glandular swellings; and that a plague in rats usually precedes plague in human beings. In addition, therefore, to prompt notification of plague patients, a system designed to obtain information as to the occurrence of plague in *rats* should be instituted. Every rat destroyed must be bacteriologically examined.

For the detection of plague-infected houses, guinea-pigs, which do not harbour fleas as a rule, are turned loose in warehouses as convenient traps for rat-fleas.

In India the compulsory inspection of all dead bodies prior to burial has been found a valuable measure for discovering infected houses and localities.

Destruction of vermin and other measures in anticipation of the introduction of plague virus.—The campaign against rats is usually carried on by the employment of rat-traps and rat-catchers, and the cautious laying down of poisons such as arsenic, phosphorus, and baryta. As no one method is satisfactory, it is usual to employ several at the same time. The pumping of SO_2 gas under pressure is useful for ships and for warehouses. So long as the sulphurous-acid gas is dry and is not used on damp articles, no damage is done to merchandise. Care has to be taken with damp things, as they may get discoloured.

Where possible, houses and warehouses should be made rat-proof — not an easy measure, considering the burrowing and climbing habits of the rat. *Rattus norvegicus* can penetrate ordinary lime-mortar or soft brick, but is stopped by cement and concrete. Its burrows may attain a depth of 18 in. *Rattus rattus* is not so active in this

respect. Simpson recommends that walls should be at least 6 in. thick when made of hard brick or concrete, and that they should extend to not less than 18 in. below the level of the ground floor, and the latter should be paved with concrete 8 in. thick, covered with ½ in. of cement. All ventilators should be protected with iron gratings, and all openings around wires and pipes cemented. In New Orleans some warehouses are elevated, leaving a clear open space beneath: in others an impervious wall is built around the ground floor, penetrating 2 ft. into the ground. In a third, and a most effective type, the ground floor is laid out in concrete with a protective wall round the edges sinking 2 ft. into the ground. The mooring cables of ships should be shielded in such a way as to prevent egress or ingress of rats, and all gangways should be taken up at night or when not in use. Native food-stores are, as a rule, set out on poles and can be protected from rat-invasion by the introduction of suitable wooden discs. The sprinkling of chloride of lime in the vicinity of the burrows has a deterrent effect.

In South Africa rigorous measures have been adopted by the Health Department to prevent the spread of rodent plague; they have endeavoured, apparently with success, to place a barrier in the shape of a gerbille-free belt between the mountain range and the sea. Gangs working under departmental rodent officers employ two main methods—poisoning and gassing. The poisoning is effected by spreading strychnine-impregnated grain by dropping it into gerbille burrows. Near homesteads, gassing is performed. A Capex cartridge is lighted, plunged into a burrow and the opening closed with earth. Meyer has shown that methyl bromide, sprayed at the rate of 10 c.c. per burrow-opening, is efficient in controlling burrow rodents and their fleas. Care, however, must be taken in its application.

Attempts have been made to set up in rats an epidemic disease, other than plague, which should not be communicable to man: for this purpose the bacillus discovered by Danysz was recommended by him; but experiments on these lines have not been very successful.

Prophylactic measures based on a consideration of the flea fauna.—Should further research demonstrate the inability of *X. astia* to transmit plague, it should be possible to divide a country into potential and non-potential plague zones by a survey of the rat-flea population. The energies of the Sanitary Department can by these means be focused on the danger spots.

Personal prophylaxis.—As regards the individual, all unnecessary visits either to plague patients or to plague neighbourhoods should be avoided and, if possible, prevented. The attendants on the sick ought to take care that the ventilation of the sick-room is thorough, that cubic space is abundant, and that the utmost cleanliness is practised. Nurses must not hang over patients unnecessarily; they must also be careful to seal up and cover any wounds, no matter how trifling, they may have on their hands. Stools and urine must be disinfected, and hands frequently washed. To obviate risk from wounds and to

prevent the access of fleas and similar suctorial insects, those engaged on plague duties should wear boots and have the legs protected by trousers tied tightly round the ankles or, better, by puttees. Leather gloves are advisable if there is much handling of furniture or of anything likely to abrade the skin. *Cats or dogs should not be allowed near plague patients.* In the interests of public health it is imperative to isolate all cases of bubonic and septicæmic plague and their contacts.

The attendants on pneumonic cases should provide themselves with masks of muslin, three- or four-fold, changed when at all damp, and also with goggles to protect the eyes. In pneumonic plague epidemics general inoculation with plague vaccine is advisable. In Mukden a mask of absorbent cotton-wool (16 by 12 cm.) enclosed in muslin, and retained in position by a many-tailed gauze bandage, together with goggles, rubber gloves, and cotton uniform, proved thoroughly effective. Evacuation of the people from insanitary and overcrowded dwellings and installing them in camps where better hygienic conditions can be arranged is imperative. Churches, schools and theatres must be closed. Cordons within the affected area, to limit the infection to a circumscribed portion, may assist.

Prophylactic inoculation. *Haffkine's inoculations.*—Early during the Bombay epidemic Haffkine introduced a system of prophylactic inoculation which is of proved value, both in reducing the number attacked with plague to the extent of from 77 to 85 per cent., and in diminishing by 80 per cent. the mortality in those attacked. It consists essentially in the subcutaneous injection of six-weeks'-old cultures of plague bacilli incubated at 25–30° C. and killed by heat—65° C. for one hour; carbolic acid 0·5-per-cent. is then added; up to 4 c.c. are injected according to the size and age of the individual. The Indian Plague Commission reported strongly in favour of these inoculations, which furnish a protection that lasts about twenty months. Glen Liston stated that in the inoculated the incidence of plague was 8 per 1,000 of the population concerned, whereas it was 34 per 1,000 in the uninoculated in the same communities; the case-mortality in the inoculated was 39·5 per 100 attacked, in the uninoculated 78 per 100. The best results are obtained from a two-months' growth which has been stored about eighteen months. The prophylactic needs great care in its preparation. Its storage in hermetically sealed bottles should be insisted upon, and every bottle ought to be tested before use. The resulting reaction is sometimes severe. The efficacy of the vaccine depends upon the virulence of the bacilli composing it; cultures made from non-virulent strains are useless from the prophylactic point of view. The potency of plague vaccine is enhanced by the incubation of plague cultures at 37° C. in place of 26° C.

So far, Haffkine's prophylactic is the one most frequently used and gives the best results. In 1927, 90,000 inoculations with plague vaccine prepared at the Entebbe laboratories were administered in Uganda. As an index of its efficacy it was noted that amongst 232

cases subsequently attacked by plague the recovery-rate was 40 per cent.

Those in attendance on plague patients should receive 20 c.c. of Yersin's anti-plague serum, and 3 c.c. of Haffkine's vaccine on the same day; ten days later a second dose of vaccine should be given. Attendants should wear lysol-impregnated gowns fastened at the wrist, ankles and neck, rubber gloves and gum-boots. They should not shave, but they should disinfect themselves and their clothes daily.

Prophylactic inoculation with *avirulent living plague bacilli* has been practised in Java by de Vogel and Otten. The smooth variety on culture has been used as antigen, and 400,000 persons were immunized in this manner without incident or accident. The plague strain "tjiwidej" which is employed was discovered by accident, and is so avirulent that both rat and guinea-pig can withstand a whole culture when inoculated. The animal experiments, as regards the production of immunity, with this living vaccine are much superior to those obtained with dead cultures. Otten's method was commenced in 1935 and up to date 2,363,642 inoculations have been carried out. Excellent results have been obtained and the present decline in the epidemic is attributed chiefly to this vaccine. Girard has now reported upon similar results obtained with his living vaccine in Madagascar.

In Indo-China a dead plague vaccine made by the Pasteur Institute is used; in French West Africa a lipovaccine and an aqueous vaccine of the Pasteur Institute (BST) is favoured.

An oral plague vaccine (*Pestedo*) has been prepared by Poulenc Frères and is well taken by natives who object to inoculation, but the results are unsatisfactory.

Description of the Commoner Species of Rats concerned in the Spread of Plague

The spread of plague and epizootics amongst rats seems to be by the fierce *R. norvegicus*. The more delicate *R. rattus* receives its infection from the sewer rat. Both these species are pestigenic. When the rat dies the fleas desert the body and seek a new host; thus the sewer rat (*R. norvegicus*) dies in the basement; the fleas attach themselves to the black house rats (*R. rattus*), and are spread to human beings.

Terms employed.—Rodents which are capable of being infected with plague are divided into *pestiferous* and *pestigenic*; thus the common mouse is a pestifer, but is not ordinarily a transmitter. *Selvatic* plague is the plague of the hinterland. In North Africa, for instance, plague of the "bled" of Tunisia has been regarded as selvatic and due to desert rodents; further south in the Sahara a mouse (*Psammomys roudairei*), though predominant and a very susceptible animal, has hitherto not been affected.

An intimate knowledge of the appearance and habits of the many species of rats is hardly necessary to the tropical specialist: considering the important rôle several species play in the spread of plague he should, however, be able to identify the more domestic varieties. For this purpose the following Table, contributed by Mr. M. A. C. Hinton, will be found useful:

Rattus rattus, Linn.—Build slender; muzzle sharp; ears large, translucent; tail usually much longer, never much shorter than head and body; hind foot (heel to tip of longest toe, without claw) 35–40 mm.; weight of adults rarely more than 8 oz. Indigenous, wild, more or less arboreal in Indo-Burmese countries. The chief domestic races are distinguished as follows:

A. Back reddish or greyish-brown.
- *a.* Under parts pure white or pale lemon. *R. r. frugivorus* Raf. (= *tectorum*). Common in Mediterranean region. *R. r. kijabius*. Uganda.
- *b.* Under parts darkened.
  - *a*[1]. Ventral hairs with rusty tips. *R. r. rufescens* Gray. Common rat of Indian houses.
  - *b*[1]. Ventral hairs without rusty tips. *R. r. alexandrinus* Geoff.

B. Back black; under parts dusky or slate-grey. *R. r. rattus* Linn. Essentially a domestic form which has been evolved in cold temperate countries.

The forms *frugivorus*, *alexandrinus*, and *rattus* have now acquired an almost world-wide distribution; *frugivorus* is the least, *rattus* the most modified race. These are climbing rats, common on ships; frequent in dwellings in warm countries, and not shunning man; they are of especial importance as plague-carriers; attain sexual maturity early (min. weight sex-mature = 70 grm.); breed throughout the year; gestation about 21 days, but with concurrent lactation about 31 days; litter of from 4 to 11; average litter 5 or 6.

Rattus norvegicus, Berkenhout (= decumanus).—Robust; muzzle blunt; ears small, opaque; tail noticeably shorter than head and body; hind foot 40 to 45 mm.; weight of adults commonly 17 oz., often much more; colour brown or grey above, silvery below. A melanic form (often confused with *R. rattus*) quite common.

Indigenous to Central Asia; now common in all temperate countries. Infests drains and waterways; common in cellars and basements, but shunning mankind as a rule. Breeding and gestation as in *R. rattus* (min. weight sex-mature = 100 grm.); litter of from 6 to 23; average litter 8 to 10

Rat Destruction (Deratization)

Terriers may be used, the rats being driven out of their holes by flooding from a watercart. Cats are useful, but it must be remembered that they too are susceptible to plague. Traps of all descriptions are of value, and rats readily enter a funnel-shaped trap showing a light at the far end. Runs may be made with double closing doors, or gins or nipper traps may be placed in the path of rat-runs. One man can attend to 100 to 200 traps a day. In towns and ports where plague exists, 40 to 50 traps should be set per day per 1,000 inhabitants. Rats which are caught alive must be asphyxiated and

then combed for fleas. The flea is placed for twenty-four hours in pure phenol to make it transparent, so that species and sex may be determined. The total number of fleas divided by the number of rats gives the "flea-index."

One of the modern methods of rat destruction is the use of lithographic varnish or "ratsticker." The varnish is spread on a board in a place frequented by rats, with a piece of cheese or other material as a bait. On coming into contact with this substance, the rat becomes hopelessly entangled and its squeals attract other rodents to the rescue, so that they in turn become trapped. Rat traps should not be handled, except with gloves. They may be covered with mud or anointed with oil of aniseed, which removes the human smell.

Baits.—A good bait is one which differs from food usually found on the premises. In fish shops, meat, cheese or bread should be used. In grain stores, bloaters, cheese, etc. Dry bread is always acceptable, while oatmeal and tallow can also be used. It is said in the tropics that tomato is specially tempting.

Poisons.—*Squill (red squill)* pancakes are made with beef dripping to which has been added 20 per cent. of finely chopped *Urginea maritima* (red variety). The pancakes are cut into baits each ½-inch square. Various squill preparations are on the market. Squill is mixed with equal parts of milk, and 8 lb. of bread, soaked, for every gallon of solution. The toxic dose for a rat is 1.30 c.c. of a liquid extract. Its action on the rat is slow; the first symptoms being excessive purging, thirst, and general discomfort, followed by paralysis and convulsions. Death is hastened by drinking. The ground-up bulbs make the best bait. On the basis that a rat eats one-tenth of its body-weight every 24 hours, each bait should consist of 60 gr.

Powdered squill is quite dangerous to handle and liquid extract is the safest preparation. Bowls of milk accessible to rats alone, poisoned with this, are effective. In autumn female rats are especially attracted by them.

Barium carbonate, 1–2 gr. kills a rat. Cats and chickens can stand 10–15 gr., whilst dogs can take 100 gr. This poison drives rats to seek water so that they die in the open. A 10–50 per-cent. mixture of barium carbonate with fatty basis (*i.e.* tallow) forms one of the safest and most effective rat poisons. "Zelio" paste or poisoned grain (Bayer) in which the grain is thoroughly soaked is said to be absolutely tasteless and readily eaten by rats. The bait is set at night and removed in the morning. After touching the poisoned bait the hands should be washed.

Effective, but dangerous to stock.—(*a*) Strychnine and barium Battle's vermin killer. (*b*) Arsenic and barium—"Rough on Rats." (*c*) "Extermo," "Rodine," "Farmer's paste," "Roth's paste," and "Sandford's paste" (*phosphorus*).

Partly effective but dangerous to man.—The virus of Danysz and similar viruses, which are bacillary in origin, vary very much in lethal effects and have been known to cause "choleraic" symptoms in man. In the tropics they require frequent subculture.

Various poisons for use in selected cases.—(*a*) Arsenic, 20 per cent. with meal. (*b*) Dish of oatmeal mixed with sugar, grated Parmesan cheese, and a small quantity of strychnine. (*c*) Dish of chicken heads. A pinch of strychnine should be placed in each neck with a drop of blood.

Cultures.—Danysz virus and other bacilli have been used with the object of causing epizootics in these rodents, but they have not been successful on the whole. In South Africa similar attempts have been made to extirpate

the gerbilles by an organism known as the Tiger River disease (*B. monocytogenes*) (E. G. Murray), and this has been partially successful.

Fleas

Readers seeking information upon the natural history and classification of these insects are referred to p. 1017.

CHAPTER XII

TULARÆMIA (Francis, 1921)

Synonyms.—Deer-fly Fever ; Pahvant Valley Plague ; Rabbit Fever ; Ohara's Disease.

Definition.—Tularæmia is a specific infectious disease of rodents, caused by *Bacterium* (*Pasteurella*) *tularense*, and is transmitted from these animals to man by the bite of infected blood-sucking insects, or by the handling or dissection of infected jack-rabbits. From group agglutination tests it would appear that *B. tularense* is closely allied to the *Brucella* group.

History and geographical distribution.—*B. tularense* was discovered by McCoy and Chapin in 1911 in a plague-like disease of rodents, more especially the ground-squirrels, of California. As far as is known, the disease is at present confined to the States of California, Indiana, Kentucky, Ohio, and Utah, in the United States. Although first found in Tulare County, California, by 1928, 650 cases had been reported in all States in the Union, with the exception of Wisconsin, Washington and the New England States. In Russia, the disease has been noted in native hunters of the musk-rat and the water rat, which are killed for their fur, and the Russian observers have noted that the infection is widespread amongst rodents in places where no examples of the human disease have been identified ; it appears that occasionally tularæmia may occur amongst sheep. In 1925 it was found by Ohara to exist in man in Japan. In 1931 it appears from the epidemiological reports of the League of Nations that the disease has been recognized both in Russia and in Norway, whilst Olin and Sehlstedt have recognized 31 cases in Sweden. The source of infection is the hare, and *Chrysops discalis* the transmitter. Diseased squirrels may also be responsible. Tularæmia has now been recorded in Germany (1931, 1933 and 1936), Lower Austria (1925 and again in 1936), Czechoslovakia (1936), and Moravia, as well as in Turkey in Europe (1936, at Luleburgaz in Thrace). In South Moravia, thirty to forty-five days prior to the notification of human cases, a great mortality was reported among field voles and hares.

Epidemiology and endemiology.—In its endemic areas the disease is most prevalent in the months of June, July, and August, when it is conveyed by a blood-sucking fly, *Chrysops discalis*, from one infected jack-rabbit to another. In this manner the disease is usually transmitted to man. Tularæmia is a disease of the rural population, particularly attacking field workers, but it has also been recorded among dealers in rabbits who handle infected jack-rabbits,

and those who prepare their skins for market. In 1924 Parkes and Spencer found that the tick (*Dermacentor andersoni*) could act as a host and as vector of the disease in man and in rodents, and demonstrated that hereditary transmission takes place in this tick. They further showed that the rabbit tick (*Hæmaphysalis leporis-palustris*) acted as a vector of the virus in rodents. Olin studied a serious outbreak of 115 cases in Sweden in 1937 which occurred especially among peasant women, who in summer-time go bare-footed and who are stung by numerous mosquitoes, and he considers that these insects may act as vectors. Four species of *Aëdes* and one of *Theobaldia* have been shown under experimental conditions to transmit the disease to guinea-pigs.

Ætiology.—*B. tularense* is a small non-motile, Gram-negative organism, measuring 0·3–0·7 μ in length; when stained in the tissues it gives the appearance of being surrounded by a capsule. Though normally occurring as a rod-like structure, it frequently assumes a coccus shape. It stains best in tissue preparations with Giemsa's stain, but in smears from cultures it shows up well with aniline gentian-violet.

The organism is difficult to cultivate; it will not grow on plain agar or in bouillon, and, until recently, had been cultivated only upon the coagulated yolk of hen's eggs, but Francis has succeeded in getting an abundant growth upon serum-glucose-cystine agar. The cystine medium is inoculated with the heart's-blood of the infected animal, or a small piece of the liver or spleen is rubbed on the surface and allowed to remain in contact with the medium. Growth appears about the third day, and flourishes luxuriantly on subcultures without the addition of fresh animal tissue. In order to ensure the primary growth, it is necessary that a piece of animal tissue be added to the medium.

Composition of cystine agar.—Cystine agar consists of beef-infusion agar, having a *p*H of 7·6, to which 0·02 per cent. of cystine is added, after which it is sterilized for fifteen minutes in a steam sterilizer, and subsequently incubated for twenty-four hours to ensure sterility.

Cultures of *B. tularense* are extraordinarily infectious, and should be handled with great care.

In its serum reactions cross-agglutination occurs in connection with *Brucella melitensis* and *Br. abortus*. About 23 per cent. of tularæmia sera do so, and about 35 per cent. of undulant fever sera agglutinate *B. tularense* to some degree.

The organism is pathogenic for guinea-pigs, rabbits, white rats, mice, ground-squirrels (*Citellus beecheyi*), gophers (*Thomomys battæ*), and *Rhesus* monkeys; while Norwegian rats (*R. norvegicus*), calves, pigs, goats, cats, dogs, and pigeons are found to be refractory. The organism is transmitted in a mechanical manner by *Chrysops discalis*, as well as by the stable-fly, *Stomoxys calcitrans*, the bed-bug, *Cimex lectularius*, the squirrel-flea, *Ceratophyllus acutus*, the rabbit-louse, *Hæmodipsus ventricosus*, and the mouse-louse, *Polyplax serratus*.

Ticks can also act as vectors—*i.e.* *Dermacentor andersoni*, *D. variabilis*, *D. occidentalis*, *Ixodes ricinus*, var. *californicus*, Banks, and the rabbit tick (*Hæmaphysalis leporis-palustris*).

The disease occurs as a natural infection in wild rodents. The most important reservoirs of infection are the cotton-tail rabbit (*Sylvilagus*), the jack-rabbit (*Lepus*), and the snowshoe rabbit (*L. bairdi*) ; other reservoirs are the Californian ground-squirrel, wild rats, and meadow mice (*Microtus californicus*). It is probable that the opossum and coyote may play a part ; also the ruffled grouse (*Bonasa umbellus*) and the sage hen (*Centrocercus urophasianus*) (Montana). In fact this disease has been responsible for the disappearance of these beautiful birds in parts of America.

Man is extremely susceptible to infection from animals, consequently laboratory infections are very frequent.

The nasal secretion and the urine of infected mice and rabbits are infective for other animals.

Of the vectors, the tick (*Dermacentor andersoni*) is particularly important, since the *Bacterium* is found distributed throughout the body, being found in the lumen of the gut, in the cells of the gut wall, in the body fluids, and in the fæces. The organism is harboured throughout the winter months and infection is transmitted to its eggs.

Pathology.—The pathological appearances of infected guinea-pigs and rabbits at autopsy much resemble those of plague in the same animals. In an experimentally-infected guinea-pig there is hæmorrhagic œdema at the site of inoculation, with blood-stained peritoneal exudate, and diffusely enlarged spleen, in which characteristic small necrotic foci can be found. Similar lesions may be detected in the liver ; on microscopic section of these organisms a dense infiltration with polymorphonuclear cells can be found, but the organisms can with difficulty be detected. In the spleen of the mouse, on the other hand, little or no leucocytic response occurs ; and when stained with Twort's light-green neutral-red stain, *B. tularense* can be readily demonstrated in large numbers. The incubation period appears to be from one to ten days.

Symptoms.—Unrecognized cases of tularæmia are probably common in the endemic areas, for it may occur as a generalized disease without local lesions, or local lesion smay be present with a secondary lymphadenitis, which may not cause grave constitutional disturbances. As a rule, in the cases which have been so far recorded, a definite type of fever is present. The onset is sudden, with headache, backache, and fleeting pains, remarkable lassitude, and pyrexia which may last for three weeks or more ; the extreme range of temperature is about 104° F. The pyrexia may subside to normal, or nearly so, from the third to the sixth day. The pains commence at some particular point, and persist for two weeks to a month, though localized ones of greater or lesser degree may recur for the succeeding twelve months. Epistaxis and dizziness are common ; the weakness and lassitude persist for

weeks after the pyrexia has subsided, and it may be months before the normal health is restored. The spleen is not palpable.

Such is the description of the generalized disease as it is met with in man. When infection results from inoculation, the effect is purely local; an inflamed papule occurs at the site of inoculation, with secondary lymphadenitis. Following the bite of an infected chrysops or other fly on some exposed surface of the body, the onset is sudden, with pains and fever. The initial ulcer presents a process of diffuse necrosis with infiltration of the base. Sometimes subcutaneous nodules resembling sporotrichosis appear on the anterior and posterior aspects of the forearm and along the lymphatics between the ulcer and the regional glands. They are firm, movable and tender, and 4–10 mm. in diameter. The patient may be prostrated and have to retire to bed; the lymph-glands draining the bitten area subsequently become inflamed and swollen, and suppuration may occur.

Infections of the eye and conjunctiva, causing acute conjunctivitis, have been recorded by Vail, Lamb, and others. In America an ocular-glandular process is well recognized. The primary lesion is of the conjunctiva and there is a regional lymphadenitis of the head and neck. There is severe conjunctivitis with chemosis and œdema of the lids and surrounding tissues. There is now little doubt, as pointed out by Herrenschwand (1935), that "Parinaud's conjunctivitis," first described in Paris in 1889, is none other than ocular-glandular tularæmia. Parinaud recognized that it was infectious and that it was associated in some manner with animals. It is characterized by the granular condition of the lids, with chemosis of the conjunctiva, inflammation and enlargement of the preauricular lymphatic glands. In 1917 and again in 1918 Herrenschwand observed two cases in Austrian soldiers, and isolated a bacillus pathogenic to guinea-pigs (undoubtedly *B. tularense*); a small portion of a culture, accidentally dropped into the canthus of the eye, immediately produced the typical conjunctivitis. In 1912 McCoy and Chapin noted a conjunctivitis in California associated with ground-squirrels, and this was undoubtedly the same condition.

Three cases of laboratory infection of tularæmia have been recorded in England. Though the debilitating effect is very marked, only one death in a series of seven cases reported from Utah has been recorded, and this took place from apical pneumonia. There is, apparently, a lasting immunity in man. There is no record of a second generalized attack, though, as in the case of Francis himself, a local reinfection may occur.

Diagnosis.—The diagnosis is most readily effected by inoculating material from the patient's ulcer, or gland-juice obtained by aspiration, into guinea-pigs, mice, or rabbits, thereby producing generalized disease in these animals, when the organism may be isolated with ease from their tissues on special media. The organisms are rarely present in the blood of human cases. Agglutination tests can readily be

performed : the serum of patients suffering from the disease will agglutinate suspensions of the organism in high dilutions, but, as pointed out by Ledingham, where cultures of *B. tularense* cannot be obtained, the spleens of infected mice contain the organisms in such large numbers that an emulsion may be made of that organ in formalinized citrate solution. On centrifuging this there may be a dense deposit of organisms, which can be used for the purpose of agglutination.

The diagnosis of this condition has to be made from plague and from rat-bite fever. In both cases alike it depends upon the recognition of the respective specific organisms.

Treatment.—This is symptomatic only. The patient should be kept in bed for several weeks after the subsidence of the fever. Convalescence should be prolonged.

Prophylaxis.—Prevention depends in part upon the avoidance of contact with infected rabbits in the endemic area. The dangers of experimental work with *B. tularense* in the laboratory have already been sufficiently emphasized. The prevention of the disease, from the public health point of view, should not cause any great difficulties. Sick or dead rabbits must be handled with great caution, and rubber gloves must be worn by laboratory workers, marketmen, cooks, etc., in view of their great liability to infection. Cooking destroys the infection, as does also prolonged freezing.

CHAPTER XIII

MELIOIDOSIS

Synonyms.—Stanton's Disease; Pneumo-enteritis; Pseudocholera.

Definition.—This is a rare, glanders-like disease occurring in Burma, the Malay States and possibly Ceylon. The name melioidosis was suggested by Stanton and Fletcher in order to describe its close relationship to glanders (Greek, *malis* or *melis*). According to Alcock, the correct but inelegant terminology ought to be "melidoidosis." A monograph on this disease was published by the above-named workers in 1932.

History.—This disease is due to *Bacterium* (*Pfeifferella*) *whitmori* (Whitmore, 1911), found at autopsies of beggars in Rangoon. In 1917 Stanton and Hennessy found similar organisms in patients dying from choleraic symptoms. According to Krishnaswamy the disease is specially common in Rangoon. Other cases have been found in Singapore and at Saigon and, according to Duke, it may occur in Uganda. In 1913 the infection appeared as an epizootic amongst the laboratory animals at Kuala Lumpur.

Ætiology.—*Bacterium whitmori* closely resembles *B. mallei*. It is a small bacillus about the same size and shape as the latter organism, and occurs in very large numbers in all the acute lesions of the disease. In films stained by Leishman's method, bipolar staining is very common. On culture also it resembles the glanders bacillus very closely, but it is more actively motile and liquefies gelatin more rapidly. It grows luxuriantly upon peptone agar, forming a dense wrinkled culture, especially when the medium contains glycerin; on broth cultures a pellicle is formed. Brown, Duncan and Henry have shown that *B. whitmori* can be distinguished from *B. mallei* by means of its behaviour on a peptonized medium containing 1-per-cent. sodium fumarate. This organism is pathogenic for most laboratory animals; for guinea-pigs, at any rate, the infection is more rapidly fatal than is glanders, but in each case, in the male guinea-pig, acute orchitis is produced on intraperitoneal injection—the so-called Strauss reaction.

The organism is excreted in the urine and fæces of infected laboratory animals, while several cases of natural infection in these animals, especially rats (*Mus griseiventer*, Bonhote), cats and dogs, have been observed. In 1927 the first case was reported in a horse from the Malay States, when the bacillus was isolated from pus from the nose.

Pathology.—The lesions produced appear to vary very considerably. Apparently, numerous small pulmonary abscesses, roughly resembling those of miliary tuberculosis, are produced. Nodules which coalesce and break down into abscesses are found in the liver; they somewhat resemble those of portal pyæmia, and have to be distinguished from amœbic abscesses. The organisms have been recovered from the blood, urine, sputum, and fluid from cutaneous vesicles of patients dying from the disease.

Symptoms.—The accounts so far published of the symptomatology are meagre. The first cases observed by Stanton in 1917 were suffering from an acute diarrhœa, with collapse roughly resembling that of cholera, and it appears that several patients who recovered from the initial intestinal attack died later from a form of septicæmia with pulmonary lesions resembling tuberculosis. During 1921 a few more cases were encountered, with similar symptoms. Only two patients are known to have recovered. There is usually a high remittent and somewhat irregular pyrexia. Delirium and mania appear to be frequent terminal symptoms. What appears to be a chronic form of the disease is also known; in this the lesions are confined to the skin and subcutaneous tissues, leading to cutaneous abscesses and collections of pus in the liver, lungs, and spleen. The initial signs may be those of acute parotitis. Very few cases have been recognized in women, but in them the brunt of the disease falls upon the bladder and the kidneys. The disease is said to be specially common in morphia injectors, but this is probably a coincidence. How man is infected, as a general rule, is still uncertain.

Diagnosis.—This is obviously best carried out by isolation of the bacillus from the fæces, urine, or blood, and differentiating it from the glanders bacillus. In one instance the organism was obtained from the cerebro-spinal fluid (P. H. Martin). Stanton and Fletcher report that the blood-serum agglutinates cultures of the organism in high dilution (1 : 2500 to 1 : 3000), a fact which is extremely useful in diagnosing the disease. Differential diagnosis from malaria, typhoid, dysentery, general tuberculosis, plague, cholera and even liver-abscess, may be necessary.

Prognosis.—Most patients die within ten days of the onset; in chronic cases they may be ill for three to eight months or more.

Treatment.—Cases were treated by Stanton with autogenous vaccines, which are said to modify the acuteness of the disease.

CHAPTER XIV

THE UNDULANT FEVERS (BRUCELLOSIS)

Preliminary statement.—Originally the term undulant fever was employed to designate a type of fever, commonly found in Malta and the Mediterranean area generally, which was usually referred to in medical literature as "Malta fever." Recent experience, however, has shown that several closely allied fevers are to be classified under this heading. These fevers are due to infection by organisms of the genus *Brucella*. The following varieties of these organisms and their associated fevers are now recognized :

1. *Brucella melitensis* (formerly known as *Micrococcus melitensis*) which is originally a parasite of the goat and which is usually conveyed to man in goat's milk.
2. *Brucella abortus* (formerly known as *Bacillus abortus*, Bang) which is an affection of the cow, in which it causes abortion. A strain (*Brucella suis*) also occurs in the pig.[1] The infection appears to be conveyed to man through cow's milk.

Although *Brucella melitensis* infections have more or less a tropical and subtropical distribution, those of the abortus type are now found all over the world, wherever epidemic abortion amongst cattle occurs.

I. UNDULANT FEVER (MELITENSIS TYPE)

Synonyms.—Febris Undulans ; Malta Fever ; Mediterranean Fever.

Definition.—A disease of low mortality, indefinite duration, and irregular course, undulant fever is the result of infection by a specific germ—*Brucella melitensis*. In its more typical form it is characterized by a series of febrile attacks, each individual one, after lasting one or more weeks, gradually subsiding into a period of absolute or relative apyrexia, also of uncertain duration. Common and characteristic complications are a rheumatic-like affection of joints, profuse diaphoresis, anæmia, liability to orchitis, and neuralgia. Although only occasionally fatal, the disease is a fruitful source of inefficiency and invaliding.

History and geographical distribution.—Formerly confounded with typhoid and malaria, undulant fever has been established as a separate

[1] Another species of Brucella is found in pigs (*Br. bronchisepticus*)—but there is no reason to believe that it is communicable to man.

disease by the labours of various observers—Bruce (1887), Hughes, Gipps, Wright, Semple, and Bassett-Smith. Undulant fever appears to be more widely distributed than was formerly thought to be the case. It is not confined to Malta, or even to the Mediterranean; it occurs in Italy, France, Spain, the Red Sea littoral, India (Punjab), China, South Africa, Somaliland, West Africa, the West Indies, the Philippines, South America, and the United States, especially in New Mexico and Texas. Owing to the close relationship between *Br. melitensis* and *Br. abortus* and the clinical resemblance between the two forms of fever they produce in man, it is extremely difficult to state the exact geographical range of each.

Epidemiology and endemiology.—The following figures, supplied by Bassett-Smith, show the importance of undulant fever in former years to the British naval and military services in the Mediterranean:

INCIDENCE OF UNDULANT FEVER

	Army			Navy			Total days
	Strength	Cases	Deaths	Strength	Cases	Deaths	sickness
1900	9,203	171	10	14,250	356	6	22,998
1901	9,384	288	10	14,070	286	3	16,987
1902	10,889	198	10	18,470	436	3	27,432
1903	10,608	507	11	18,410	400	6	30,541
1904	10,615	429	15	19,590	430	9	28,458

The most susceptible age is between the sixth and the thirtieth year. Length of residence does not influence susceptibility. In Malta the natives suffer as well as visitors, while there and in other places where the disease is endemic it occasionally assumes an epidemic character. The period of its greatest prevalence is the season of lowest rainfall, embracing June, July, August and September, the disease differing in this respect from typhoid, which, in Malta, is more prevalent during the succeeding months, but cases may occur all the year round. This is explained, not only by the greater use of milk during the summer months, but also by the fact that, following the birth of the kid in spring, contamination of the milk is more marked. The goats are not necessarily ill at all, excepting for their liability to abort. The disease tends to occur in particular towns or villages, in particular houses, barracks, hospitals, and rooms, and in particular ships, manifestly originating in limited foci of infection. Certain ships were notorious foci of the disease. All classes were liable: the officer and his family as well as the soldier in barracks or the sailor on shipboard. The organism has been found in mother's milk, so may presumably be transmitted to sucklings.

It is not exactly correct to assume, as has so often been done, that because of these essential discoveries, undulant fever has been banished entirely from Malta. The cases amongst the British military and naval population dropped from 245 in 1905 to 12 in 1907, but during the years 1929–35, there was a great increase in the number of cases among the civil population. Gatt (1938) reports that among the latter the

incidence of the disease increased till 1934, when as many as 7·25 per mille were infected. Among the indigenous inhabitants there is a deep-rooted prejudice against boiling of the milk, and they are not content unless the goats are actually milked on their doorstep. However, tinned preserved milk is coming rapidly into favour among the poorer inhabitants as an infant food.

Although the possibility must not be ignored, undulant fever is not generally transmitted directly from one person to another; that is to say, is not, as a rule, directly communicable from the sick to the healthy. The germ is readily conveyed by inoculation; the prick of a contaminated needle will suffice. Moreover, it is a well-recognized fact that undulant fever is the most easily acquired in the laboratory from the handling of cultures. Living emulsions of the micro-organism should never be handed round for class work; similarly, infection may be conveyed by sucking a thermometer recently used by a patient. A very striking circumstance is that in some hospitals the nurses and attendants in the fever wards are ten times more liable to contract the disease than people not so employed.

Milk.—It is now known that the infection is most usually conveyed in milk, and it has been suggested that it may be introduced in other kinds of food, or in water. Facts pointed very distinctly to goat's milk as the most important medium. The organism was present in the milk of 10–50 per cent. of Maltese goats, and monkeys were easily infected by feeding them on it. Immediately on the goat's milk supply to the naval and military hospitals in Malta being stopped, the cases of locally acquired undulant fever practically ceased. Formerly this fever was very common in Gibraltar. The milk supply of the garrison at that time was largely from animals imported from Mata. Gradually these goats have died out or been got rid of, and no more have been imported. Concurrently with this there has been a marked and proportional reduction of undulant-fever cases in the garrison, so that as a cause of disability it has now quite disappeared from the records of the Army and Navy there. There is one well-authenticated instance of wholesale infection from this source in the case of the s.s. *Joshua Nicholson*, which shipped 65 goats in Malta; an epidemic of undulant fever broke out on board, and nearly all those who drank the milk of the goats were attacked.

Cheese.—There is a considerable amount of evidence that undulant fever can be acquired by eating cheese made from the milk of infected goats. Several varieties of cream cheese made in the South of France, and even ripened cheese such as "Camembert," have fallen under suspicion.

Manure.—In the department of Aude near the Pyrenees, cutaneous infection by manure soiled by urine of infected goats and sheep is regarded as possible.

Ætiology.—Bruce in 1887 demonstrated the presence in the spleen in undulant fever of a special bacterium—now called the *Brucella melitensis*, and by a series of experiments proved that it was the cause of the disease.

Unfortunately, as the bacterium occurs only sparsely in the general circulation (unless in the earlier stages, when the temperature is high), to search for it in the blood in the later stages of the disease does not aid in diagnosis. The organism is present in abundance in the spleen pulp, and also in the lymphatic glands, in which it persists longer than elsewhere, and from both of which it can be recovered by cultivation. Bruce found it in the spleen in ten fatal cases. His results have been confirmed by many other observers. Injections of pure cultures give rise to a similar disease in monkeys and other animals, from whose blood the bacterium can be recovered, cultivated afresh, and injected into other animals, when it will again give rise to the disease. In five recorded instances, inoculation—intentional and accidental—of cultures of the bacterium into man has been followed by the characteristic symptoms after an incubation period of from five to fifteen days.

A variety of the organism, *Brucella paramelitensis*, which gives different serological reactions from those of the original strain, has been recognized as responsible for those cases of clinical undulant fever in Tunis and Algeria which do not give an agglutination reaction with cultures of *melitensis*.

Br. melitensis measures 0·33 μ in diameter. It occurs generally singly, often in pairs, sometimes in fours, but never, unless in culture, in longer chains. It is Gram-negative and readily stained by a watery solution of gentian-violet, and is best cultivated in a $1\frac{1}{2}$-per-cent. very feebly alkaline peptonized beef agar; in this medium, some time after inoculation, it appears as minute, clear, pearly specks. After thirty-six hours the cultures become a transparent amber; later they are opaque. No liquefaction occurs in gelatin. The individual colonies are small, round, somewhat raised discs growing to 2–3 mm. in diameter about the ninth day. The optimum temperature for growth is 37° C. In bouillon it may produce a general turbidity. As a rule, the organism cannot be cultivated under anaerobic conditions.

At one time believed to be a delicate organism, recent investigations have shown that the bacterium can live for a long time in water, in dust, or on the clothes of patients, and that it is not killed by cold or desiccation. Moreover, it is now known to be excreted in the urine of man in 10 per cent. of convalescent cases, and to occur in great abundance in the milk and urine of apparently healthy Maltese goats (50 per cent.), and probably of cows. It is also found in dogs (9 per cent.), sheep, and horses. These facts account in part for the great frequency and dissemination of the disease in such insanitary places as Malta, to which place they specially refer.

Br. melitensis can be cultured from the blood-stream during the height of the fever in a considerable proportion of cases; for this purpose 5–10 c.c. of blood should be withdrawn from a vein, and well diluted in flasks, each containing 50 c.c. of bouillon; these should be examined daily during a week's incubation, or even longer. Sometimes it can be grown more easily from the blood-clot, and successful isolations have been obtained after 26 days' incubation. It has occasionally been obtained from the fæces. The serum of undulant-fever cases of this and the abortus type, as well as the milk of infected goats will agglutinate it. The organism has been recovered from the gall-bladder by Eyre. Amongst the smaller laboratory animals, the guinea-pig is highly susceptible to inoculation—a minute dose injected intraperitoneally causing prolonged infection.

Br. melitensis was stated by Evans, Myer, Shaw, and others to be morphologically, culturally, and serologically similar to *Bacillus abortus* (Bang) now known as *Brucella abortus*. Three strains, *melitensis*, *paramelitensis*,

and *abortus*, are separable one from another only by means of absorption tests. Cultures of *Br. abortus* are agglutinated in high dilutions of the serum of patients suffering from undulant fever. The most satisfactory method of differentiation of the varieties of *Brucella* is agglutinin-absorption : this criterion must be applied to infections in animals and in man in order to determine their ætiology.

It is well known that *Br. melitensis* may produce abortion in goats, though the animals themselves may exhibit no other clinical changes of disease.

In monkeys intramuscular injection produces within three days a rise of temperature and death within three weeks. According to Burnet and Conseil, *melitensis* is at least a thousand times more pathogenic for monkeys than is *abortus*. Indeed, only enormous doses of *abortus* will produce any effect at all in small monkeys.

Pathology.—The disease has almost no pathological anatomy. The spleen is the only viscus which is distinctly diseased. In undulant fever this organ is enlarged (average 17 oz.), soft and diffluent ; on microscopical examination the lymphoid cells are found to be increased in number. There may be some congestion and even ulceration of the intestinal mucosa, but this is not an essential feature. Other organs show chiefly cloudy swelling, and glomerular nephritis may be present.

Symptoms.—The period of *incubation* in the naturally-acquired disease is difficult to fix. Cases have occurred as early as six days after arrival, others as late as fourteen and seventeen days after leaving Malta. Some hold that the disease may remain latent for months. It begins generally with lassitude and malaise, such as we associate with the incubation of many specific fevers, particularly typhoid. There are headache, boneache, anorexia, and so forth. Pain in the eyes, especially on lateral movement, is very characteristic. There may be a peculiar sensitiveness of the alveolar margins of the jaw and painful movement of the temporo-mandibular joint. At first the patient may go about his work as usual. Gradually the daily task becomes increasingly irksome, and he takes to bed. Headache may now become intense, and, in addition, the patient will suffer from thirst and constipation. At the commencement the symptoms, except that there is very rarely diarrhœa, resemble those of typhoid. There are no rose spots, however, then or at any subsequent period. There is evidence, in the coated tongue which looks as if covered with white paint, in the congested pharynx, the anorexia, and the epigastric tenderness, of gastric catarrh ; and the occasional cough and harsh, unsatisfactory breathing at the bases of the lungs indicate some degrees of bronchitis or of pulmonary congestion. There may also be delirium at night, but as a rule there is insomnia. The fever is usually of a remittent type, the temperature rising about midday (generally about 2 p.m.) and falling during the night, and the patient becoming bathed in a profuse perspiration towards morning. The spleen and the liver, but especially the former, are somewhat enlarged and perhaps, tender. Lumbar pain may be severe, while insomnia is a distressing feature.

After a week or two of this type of fever, specially distinguished by pains and perspirations, the tongue begins to clean and the appetite to revive; but, notwithstanding these signs of amendment, the patient still remains listless and liable to headache and constipation. He continues feverish and at times perspires profusely. Gradually, however, although the patient is anæmic and weak, subjective symptoms become less urgent; he sleeps well now, he has no delirium at night, and he can take food, and this although the body-temperature may still range slightly above the normal. Then once more, and perhaps over and over again, fever with all the former symptoms gradually returns; and now, if it has not declared itself before, the peculiar fleeting rheumatic-like affection of the joints or fasciæ, so characteristic of the disease, shows itself in a large proportion of cases. One day a knee is hot, swollen, and tender; next day this joint may be well, but another is affected; and so this metastatic, rheumatic-like condition may go on until nearly all the joints of the body have been involved one after the other. The patient may suffer also from neuralgia in different nerves—intercostal, sciatic, and so on. Orchitis is an occasional early complication, and may be mistaken for testicular mumps. In some cases these complications are severe and characteristic; in others they may be mild, or absent altogether. In this respect the same infinite variety exists as in other specific fevers. In severe cases a purpuric condition with bleeding from the gums is occasionally observed. Epistaxis may occur.

The most characteristic feature of undulant fever is the peculiar behaviour of the temperature (Chart 14). In a mild case there may be a gradual ladder-like rise through a week or ten days to 103° or 104° F., and then through another week or so a gradual ladder-like fall to normal, the fever, which is of a continued or slightly remitting type, leaving for good without complication

of any sort in about three weeks. Such mild cases are the exception. Usually, after a few days of apyrexia, absolute or relative, the fever wakes up again and runs a similar course, the relapse being in its turn followed by an interval of apyrexia, which is again followed by another relapse; and so on during several months. This is the "undulant" type from which Hughes derived the name he suggested for the disease—*febris undulans*. A factor of practical importance from the diagnostic point of view is the tendency for the fastigium of the temperature curve to occur towards midday, or early afternoon (generally about 2 p.m.); this feature distinguishes it from typhoid, in which the maximum rise generally occurs towards 6 p.m., or from other long-continued septic fevers, such as that in hepatic abscess, in which this takes place towards night-time.

In cases of another class a continued fever persists for one, two, or more months, with or without the usual rheumatic, sudoral, and other concomitants—the "continued" type of Hughes.

Usually remittent or nearly continued in type, in a proportion of instances (generally paramelitensis infections) the fever exhibits distinct daily intermissions, the swinging temperature chart suggesting sepsis, endocarditis, or malaria. But there is no local evidence of suppuration; the malaria parasite cannot be discovered in the blood, the quotidian rise of temperature is accompanied by no ague-like rigor, or at most only by a feeling of chilliness, nor is the disease amenable to quinine. This is the "intermittent" type of Hughes. In other instances these types may be variously blended.

In some patients, two to three months may elapse before they are finally rid of the tendency to febrile attacks and characteristic pains and aches. According to Bassett-Smith, the average duration of the disease is four months, but it may last two years. The shortest period is about three weeks.

As in other zymotic diseases, cases of all degrees of severity are met with in undulant fever. Bassett-Smith recognized five types:

(*a*) *Ambulant*.—The patients have no symptoms, but are excreting *Br. melitensis* in their urine and are naturally potential sources of infection.

(*b*) *Mild cases*.—These last about a fortnight and are apt to be mistaken for paratyphoid.

(*c*) The *ordinary type*.

(*d*) The *malignant type*, with hyperpyrexia and toxæmia. This may be fatal, and considerable difficulty may be experienced in making a diagnosis, as in the case reported by Archibald in which death took place on the twenty-seventh day.

(*e*) An *intermittent type* with hectic fever, sweats, and general wasting. This is liable to be mistaken for tuberculosis, and appears to be common in South Africa.

Hydrarthrosis of a single joint cavity and superficial abscess formation on the chest or abdomen, without evoking a generalized fever, may also be produced by *Br. melitensis*. The Editor has seen

one such case from Somaliland in which, had not the organism been isolated from the abscess pus, this possibility could never have been suspected. Chronic infection resulting in osteomyelitis of the long bones has been recorded.

Complications and sequelæ.—As a rule, by far the most serious consequences of undulant fever are the debility it entails, the emaciation, the profound anæmia, the rheumatic-like pains, the neuralgias, and such sequelæ as abscess, orchitis, mastitis, parotitis, boils, etc. It is estimated that orchitis occurs in four per cent. of cases. It is prone to give rise to ovarian pains, dysmenorrhœa, amenorrhœa, menorrhagia, and to favour abortion and premature labour. In the male, intermittent hæmorrhages from the urethra are not uncommon. The germ may pass into the fœtus; children born in such circumstances are weakly.

Complications such as splenic and hepatic enlargement, enlargement of the mesenteric and cervical glands, suppuration, phlebitis, chorea, various psychoses, arteritis, endocarditis, melæna, hæmaturia, etc., are met with occasionally during the long course of this disease. When death occurs it is usually from suddenly developed hyperpyrexia; occasionally it is brought about by exhaustion, by hæmorrhages and purpuric conditions, or by some pulmonary complication such as pneumonia. Fatal gastric and intestinal hæmorrhages, as in the abortus type, have been described on many occasions. In a few instances the fever is a fulminating type, rapidly ending in death from hyperpyrexia.

After such a long, debilitating illness the susceptibility to tuberculosis is much enhanced.

A comparatively common sequel is chronic inflammation of the sacro-iliac joint; there may be hæmorrhages into the vesicula seminalis, a fact noted by earlier writers on this subject.

Diagnosis.—The diagnosis of undulant fever from typhoid is an important practical matter; it is exceedingly difficult in the early stages. Reliance has to be placed principally on the characteristic temperature curve, the presence or absence of rose spots, of diarrhœa, of joint complications, and of sweats, the locality where and the season in which the disease was contracted, and the agglutination test. There may be considerable hesitancy in differentiating it from pulmonary tuberculosis, especially in the intermittent form, and there are cases of undulant fever with pulmonary signs and symptoms which may resemble that disease. Again a melitensis infection may "light up" a quiescent tuberculosis.

An *intradermal* or "melitene" reaction (Burnet, 1922) has been introduced. For the purpose 0·2 c.c. of a killed broth-culture, containing half a million organisms, is injected into the skin. If the reaction is positive, a red œdematous area results at the site, and persists for several days. Adequate controls with broth and cultures of other organisms should be performed in adjacent areas of skin. According to Nattan-Larrier the melitene reaction

is best performed by injecting $\frac{1}{10}$–$\frac{1}{20}$ c.c. of the filtrate of a 20 days' broth culture into the skin 4 in. above the elbow. In typical cases the reaction, which consists of a red plaque 4–6 cm. in diameter, becomes positive in six hours and persists for two days. The reaction is positive on the seventh to tenth day of the fever and persists for ten months after recovery. It has been asserted by Wilson and others that if this reaction is repeated abscess formation may result ; even gangrene of the skin has been observed.

Hæmoculture.—As early as the second day of the disease the organism may be recovered from the blood-stream. For this purpose 1–5 c.c. of blood should be drawn off by means of an aseptic syringe and with great precaution distributed into several flasks of broth. The broth should be incubated twenty-four hours, or for as long as five days, sometimes even longer, and subcultures made from time to time on trypsin-agar slopes. On the fifth day, on further incubation, minute dewdrop-like colonies should become apparent, and the emulsion should be tested against a specially prepared immune serum in dilutions from 1 : 40 to 1 : 400. It is said that cultures from the blood-clot may sometimes give better results than those from the whole blood. The organism may be obtained by splenic puncture, though this method is rarely justifiable.

Isolation from the urine.—This is much more difficult to obtain than from the blood. The urine must be obtained either by catheter or midstream specimen after the fifteenth day of the disease. Every precaution must be taken to prevent contamination, to which *Brucella* is very sensitive.

Agglutination test.—Agglutination, if performed by the macroscopic method and with modern technique, will generally give positive results, though this reaction is not always so reliable as the Widal test in typhoid fever. There are several important points which it is necessary to remember in connection with the reaction.

Strain of organism employed for agglutination.—The serum, as a rule, contains no agglutinins till after the second week of the disease. It may be necessary to employ several strains of *Br. melitensis*, as well as cultures of *Br. paramelitensis*.

Titres of agglutination as high as 1 : 6000 have been reported in man.

As other sera are known to agglutinate the organism in low dilutions, it is recommended that the blood be heated to 56° C. for half an hour before being used for the test, in order to destroy non-specific agglutinins. The occurrence of a proagglutinoid zone (or zone of no reaction) may be a source of error, but only in higher dilutions, and it is possibly due to the presence of anti-agglutinins. It is necessary, therefore, to employ a considerable number of dilutions (*see* p. 1039).

According to Ledingham the serum of tularæmia agglutinates *Br. melitensis*. A problem of differential diagnosis may arise when a serum agglutinates both *B. tularense* and *Br. melitensis* in equal titre. This can only be settled from a serological aspect by testing for the absorption of agglutinins.

After the fever has gone on for several weeks, diagnosis is, of course, easier ; in the early stages, on clinical grounds alone and, apart from

the agglutination test, it may be, as already stated, almost impossible. Tuberculosis, abscess, empyema, malaria, relapsing fever, and all the causes of continued high temperature of a septic type, have to be carefully excluded in attempting a diagnosis. The possibility of the concurrence of another infection—typhoid, for example—must not be overlooked.

Prognosis.—As a general rule, in military and naval forces the mortality-rate is low, from 2 to 6 per cent., but in the civilian population it may be considerably higher. Death may occur from hyperpyrexia, heart-failure, or pulmonary complications. Bassett-Smith pointed out that a persistent temperature of 104° F. may indicate a grave prognosis, as may also an intermittent pulse. Alarming symptoms may develop at any stage of the disease, especially in relapses. Though it may be unwise to forecast how long a fever may last, yet when the pyrexia has subsided for more than ten days, and the patient's tongue is clean and his appetite good, no further relapses may be expected; but a short terminal rise of temperature is frequently met with.

In the malignant type of case the death-rate may be 10 per cent. or more. A persistent temperature of 104° F. and an intermittent pulse are to be regarded as grave, as are also pneumonic complications. The after-effects of the disease are often incapacitating, especially as regards the production of neurasthenia, neuralgia and cardiac weakness. The debility which results makes the convalescent an easy prey for any intercurrent disease. It is normally considered that, as a general rule, a lasting immunity is conferred by one attack.

Treatment.—When the diagnosis is sure it is well to give a purge—none better than calomel and jalap—and to instruct the attendants to keep the patient's temperature systematically below 103° F. by cold sponging with vinegar and water or, if necessary, by cold bath or by ice variously applied. In view of the prolonged nature of the fever this measure is one of importance; at the same time, such treatment need not be applied too energetically, or so as to depress: a fall of 2° or 3° is all that is desirable.

Phenacetin and similar antipyretics are also often given to bring down temperature: but the wisdom of employing depressing drugs in so chronic and asthenic a disease is, to say the least, questionable. Threat of hyperpyrexia is best met by early employment of sponging, the wet pack, or, if necessary, the cold bath. Sleeplessness may demand hypnotics, such as trional, veganin, or allonal; headache, if severe, moderate doses of phenacetin, pyramidon, or a similar drug; inflamed joints or testes, the usual local applications; constipation, enemata or aperients. In fact, the treatment resolves itself into a treatment of symptoms.

X-ray therapy.—Rudnew and Krumberg have instituted a new treatment by X-rays. The region of the spleen is irradiated for fifteen minutes with a fixed dose, filter 4 A. 1., tube 10 + 15, 2 milliampères.

Vaccine-therapy.—The therapeutic use of vaccines of dead organisms, prepared and administered according to Wright's methods, has been favourably reported on.

Autogenous vaccine.—In the Editor's experience, stock vaccines are of little benefit. The vaccine should be autogenous and prepared from the patient's organism isolated from blood-culture. In the latter instance, as a general rule, a considerable local reaction develops at the site of injection. In these cases where blood-culture has been successful the initial dose should be 50,000,000 organisms, and it should be progressively increased at three-day intervals, up to 200,000,000. In intractable cases the administration of vaccine in this manner certainly results in the lowering of temperature and in the clinical improvement of the patient's condition. Occasionally a pooled vaccine made from several different strains produces better results than does an autogenous one. According to modern conceptions of therapeutics vaccine therapy is best combined with sulphanilamide treatment.

Protein-shock therapy with non-specific protein (T.A.B.) has been found to have the effect of cutting the fever short by producing a febrile reaction with rigors (*see* p. 328).

Serum-therapy.—Sergent and Lhéritier have produced an anti-melitensis serum by intravenous inoculation of cultures into a horse. They say it is effective if given in doses of 50 c.c. on three consecutive days. It is useful in chronic as well as in acute cases. An anti-melitensis serum is also put up by Mulford, and is given in doses of from 50–100 c.c. It may be given by the intravenous route and repeated at twenty-four-hour intervals.

Sulphanilamides.—The treatment of fevers of this type with prontosil or other sulphanilamides is now being tried out. Neumann and Petzetakis report that their results are on the whole favourable. Apparently prontosil is best given intramuscularly—5 c.c. of prontosil soluble by injection for ten days, and simultaneously 1·5 grm. (3 tablets) daily by the mouth. After an interval of seven days, the oral treatment is recommenced for twenty days, and thereafter, if necessary, further treatment on the same lines is instituted. The results in children were specially favourable, and in these 4 tablets (2 grm.) are given daily for a week or ten days. Groués has further reported good results in eight cases from combined treatment with vaccine and sulphanilamides. It appears necessary that large doses of M. and B. 693 should be employed, and that the treatment should be persisted in, but the editor, from his experience does not recommend *intramuscular* injections of M. and B. 693, which may produce painful and intractable local reactions. Recent experience has shown that failure of sulphanilamides is probably due to insufficient dosage, and adults should be given 4–9 grm. daily for courses of four or five days each, what is known as "Stoss-Therapie." It is curious that infants and small children tolerate sulphanilamides better than do adults ; even a child of two months may tolerate 3 grm. daily. Toxic sequelæ are

methæmoglobinænia and a morbilliform rash. Debono (1938) in Malta, in severe cases, has been unable to find any advantages from this treatment, when he gave 4·5 grm. prontosil daily by the mouth for seven days.

Fouadin.—Neumann from Malta has reported favourably on a series of cases treated by intramuscular injections of fouadin. This is a trivalent antimony compound (pyrocatechin-disulphonic acid, *see* p. 725). Being non-irritating, it is given into the gluteal region in doses of 1·5 c.c. on the first day and 3·5 c.c. on the second, followed by 5 c.c. on alternate days. The maximum dose for women is 4·5 c.c. There is no pain at the site of injection, the drug is well tolerated, and no secondary effects have been observed. In a series of eight cases the temperature settled to normal in ten days.

The *diet* at first should consist of milk (in Malta, boiled); later, of broths and eggs and, if necessary, stimulants; but note that on *sulphanilamide* treatment the latter should be omitted. Solids must not be freely given during high fever or when the tongue is coated. If appetite is present, ordinary simple food may be taken. Lemonade or lime-juice should be given after a time; not merely as a pleasant, thirst-relieving beverage, but with a view to averting scurvy—not at all an improbable complication, if the dietary be too restricted over a long period. Feeding must be conducted with the greatest circumspection, avoiding overfeeding on the one hand and a low monotonous diet on the other. The tongue and the appetite are the best guides.

Exercise, travelling, and anything that tends to induce fatigue are prone to provoke relapse if indulged in prematurely; but a couch or chair in the garden is to be encouraged, weather permitting. The patient should rest for at least three weeks after the temperature has become normal.

Flannel clothing should be worn, and frequently changed if there is much sweating.

When possible, the subject of undulant fever would do well to avoid the endemic area for one or more years after recovery. In chronic cases a change of climate would appear to be the only therapeutic measure of value.

Prophylaxis.—Malta and those Mediterranean ports in which this fever is endemic should be avoided by pleasure- and health-seekers during the summer. Those who are obliged to live there all the year round would do well, at this season, to leave the towns and reside in places of healthy repute in the country. As a matter of precaution, in the endemic areas the drinking-water, food, and drains ought at all seasons to receive special attention. *All milk should be avoided, or sterilized by boiling*, and food dishes should be washed with boiled water. Every care should be taken to avoid insect-bites and other skin lesions. Laboratory workers must be careful in handling cultures of the bacterium; the accidental introduction of the organism into the conjunctival sac has sufficed to cause the disease.

The discovery that goat's milk is the principal medium through which undulant fever is communicated to man has led to very striking and important results. Unfermented cheese is a frequent source of infection and should be prevented. In Toulon the disease has been traced to "fromage cervelle" made from the milk of sheep and goats. Prophylactic measures should therefore be based on the considerations that epidemic abortion in cattle and undulant fever in man may be closely connected.

On the recommendation of the Mediterranean Fever Commission, the use of the milk of the Maltese goat was interdicted for the naval and military forces of that island. Immediately the incidence of undulant fever began to drop- in the Navy, from an average of 240 per annum up to 1906, to 3 in 1910, and in the Army, from a previous average of 315 per annum to 9 in 1907. In 1909 the health authorities in Malta were authorized to kill all goats whose blood or milk gave the *Brucella melitensis* reaction. The goat population of the island was consequently reduced from 17,110 in 1907 to 7,619 in 1910. Concurrently the fever incidence in the civil population fell from an annua average of 632 to 318 (Eyre). At present, consequent upon the issue of condensed milk in place of goats' milk the incidence of undulant fever has been greatly reduced in Malta (Stephens), while it has completely disappeared as a factor in the sick-list of the Army and Navy; indeed, it is correct to state that no authentic case has been recorded within the last three years.

These facts suffice to indicate the direction preventive measures should take. It must be borne in mind that certain products of milk—cheese, butter, etc.—may communicate the germ, and, further, that infected goats may appear to be in perfect health and may milk satisfactorily.

The prevalence of infected animals is best determined by cultivating the organism from their blood or milk; failing this, serum reactions (p. 317) and Zammit's test are employed. The latter, which is known as the *lacto-reaction*, consists in diluting the milk to 1 : 20 and mixing it with a dense emulsion of *Br. melitensis* or *paramelitensis*. The mixture is drawn up into a capillary tube and placed in the incubator for twenty-four hours, when any sedimentation present may be detected. It is better to heat the milk first to 56° C. for half an hour.

The proportion of infected goats has been estimated as follows:

Malta	50 per cent.
Algeria	3·4 „ „
Tunis	30·7 „ „
Marseilles	34·2 „ „

Zammit and Debono attempted to immunize the Maltese goat by employing dermal immunization. A filtrate of a broth culture is sprayed over the mammary region and into the mouth, and 1 c.c. is injected intradermally in four places. The treatment is repeated four times on alternate days.

Prophylactic inoculation.—Nicolle and Conseil conducted some experiments on man which seem to show that it is possible to immunize against undulant fever by subcutaneous injections of killed cultures of the organism, and similar results were obtained by giving 100,000,000 organisms by the mouth on three consecutive days, and again on the fifteenth day. These results were controlled by subsequently injecting cultures of living organisms; the controls in both cases developed undulant fever.

Dubois and Sollier have employed a vaccine of various strains of *melitensis* mixed with two strains of *abortus*. The complete vaccine made up of five strains contains 2,000,000,000 organisms per c.c. The first dose is 0·25 c.c. or 500,000,000; the second 0·75 c.c. or 1,500,000,000; the third 1 c.c. or 2,000,000,000. The full course of injections was given to 111 persons engaged in dealing with infected animals, and none of these developed undulant fever.

II. UNDULANT FEVER (ABORTUS Type)

Synonym.—Abortus Fever.

Definition.—A definite variety of undulant fever in man produced by *Brucella abortus* caused by infection by the organism of contagious abortion of cattle and swine.

History.—In 1878 Lehnert transmitted contagious abortion by intravaginal inoculation of pregnant cows with the vaginal discharges of aborting animals, and in 1896 Bang and Stribolt demonstrated small Gram-negative bacilli in the uterine exudate of infected cows, and isolated the organism in pure culture. This was later confirmed by Preisz (1903), Nowak (1908), McFaydean and Stockman (1909), and by MacNeal and Kerr in the United States in 1910.

In 1918 Miss A. C. Evans first showed the close relationship between Bang's bacillus and *Brucella melitensis*. Later she showed also that a close association existed between *Br. bronchisepticus*, an organism which produces a distemper-like disease in dogs and pigs. There appears also to be some connection with *B. tularense*, the organism of tularæmia.

In 1911 Schroeder and Cotton in the United States found that as the result of injecting guinea-pigs with cows' milk, 14 per cent. were infected with *Br. abortus*. In 1914 Kennedy, in London, noted that agglutinins of *Br. abortus* (which was then thought to be *melitensis*) were to be found in the blood serum and milk of London cows, and shortly afterwards this was confirmed by Bassett-Smith. These observations have been extended by Wilson and Nutt in 1926, and extensive investigations on commercial milk were undertaken by Walker Hall, of Bristol.

In 1922 Bevan suggested that a type of undulant fever in Rhodesia, which had in recent years become very prevalent on farms where there were large numbers of cattle themselves infected with epidemic abortion, was really caused by *Br. abortus*. He considered that the cow in this case was the source of infection. In 1924 Bevan's suggestions were amply confirmed by Orpen, who on comparing strains of *Br. abortus* isolated from human cases and those derived from cattle, pronounced them to be identical; in

the same year Duncan isolated in London *Br. abortus* from the blood of a Rhodesian undulant fever case. From this time onwards it came to be recognized that sporadic cases of undulant fever occurring in European countries were of the abortus type. In 1923 Aublant, Dubois, Lafenêtre, and Lisbonne found that in France between 3,000 and 4,000 persons had suffered from undulant fever within a space of three years, and in the South-East Mediterranean area they attributed the prevalence of the disease to herds of sheep infected with *Br. abortus* and the infection of man to the drinking of sheeps' milk. In 1925 the Editor described cases of undulant fever of the *abortus* type in England which undoubtedly were attributable to cow's milk. Madsen in 1928 found abortus fever widespread in Denmark. In 1926 Huddleston reported three cases of *Br. abortus* infection amongst students engaged in handling cultures in U.S.A., and in Germany there are recorded the cases of five veterinary surgeons who contracted undulant fever from abortus-infected cattle. In 1931 over 1,545 cases were notified in the United States. Horning (1935) has reported a severe outbreak of this fever in Connecticut in which *Br. suis*, the variety found in pigs, was the cause. Three cases were fatal. In this outbreak the cows had become infected with the *Br. suis* from the pig herd.

Geographical distribution.—Undulant fever of the abortus type in man has now been reported from the following countries: Italy, Canada, U.S.A., Denmark, Sweden, Germany, Holland, Switzerland, Austria, Poland, and Palestine. In England the number of cases identified as abortus fever is growing yearly, and in 1933 over 140 such were recognized and reported. Previous to this sporadic cases had been reported from time to time and an attempt had been made to ascribe them to occasional drinking of goat's milk. Such cases were reported by Byam in 1918, and by Bamforth and the Editor in 1927. Since that time the organism (*Br. abortus*) has been cultivated from the blood, urine, and fæces of man, in British cases.

Ætiology.—Traum (1914) isolated *Brucella* from a pig fœtus. *Br. suis* is transmissible to cattle and also to sheep, and Huddleston has isolated the organism from the diseased testicle of a dog. Huddleston and Hardy, in Iowa, U.S.A., have established that in that State *Br. suis* is the cause of many cases of abortus fever in man. There are many references to the concurrence of *Br. abortus* in the lesions of poll evil and of "fistulous withers" in horses. The organism is commonly associated with these lesions, but there is some difference of opinion as to whether they have not merely migrated to a suitable spot, for the filaria worm *Onchocerca cervicalis* is frequently associated with it.

In England, the cow is considered to be the main reservoir of infection. Menton (1937) found no evidence that goats or other animals are infected with *Br. melitensis* in England, although cows can be artificially infected with it, and the organism will appear in the milk. It has been shown that *Br. abortus* can be recovered from 6·3 per cent. of cow's milk.

Since the discovery of the porcine strain of *Br. abortus* (*B. suis*) the tendency in America is to ascribe human cases to this source. In the case of the pig, evidence in U.S.A. is to the effect that infection is acquired by meat packers from direct contact with the carcase. Doyle has now found that a small proportion of sows in England are infected with it.

Differentiation of ***Brucella abortus*** **from** ***Brucella melitensis*****.**—*Br. abortus* is usually somewhat larger than *Br. melitensis*, being from 0·4 μ to 0·6 μ in thickness, and varying in length from 0·8 μ to 2·5 or even 3 μ. The organism is remarkably pleomorphic ; involution forms are of unusual occurrence. The organism is isolated from the milk and uterine discharges of infected animals. Normal strains of *Br. abortus* of bovine origin cannot be grown in primary culture at the ordinary carbon-dioxide tension of the air, and to ensure growth it is necessary to raise the proportion of carbon dioxide to 5 per cent. or 10 per cent. by volume. These requirements diminish as the strain is propagated on artificial media. The simplest method of growing this organism is in a Bullock's jar in which cultures have been placed for incubation, and adding a sufficient amount of pure carbon dioxide to produce the optimum concentration.

The organism grows best on glucose agar by adding 2-per-cent. glucose to a simple meat-extract agar medium set to reaction of pH 7·4, or in Fildes' medium. On potato slopes of alkaline reaction, differences in the growth character of *Br. abortus* and other organisms of the group may be found in week-old cultures ; the former gives a uniform creamy-yellow growth, while *Br. melitensis* and *Br. paramelitensis* yield a greyish-chocolate or even black growth.

The reaction to dyes is important. The *abortus* type is inhibited by the presence of thionin in suitable concentration, the porcine *abortus* type by the presence of basic fuchsin, methyl violet, or pyronin. The bovine *melitensis* type grows in the presence of all four dyes.

The formation of hydrogen sulphide from proteins or aminobodies containing sulphur is one of the most important biochemical reactions. The organism is grown on Staffseth's liver-infusion agar medium at a reaction of pH 6·6 and, after sowing, a strip of lead-acetate paper is introduced into the tube. After forty-eight hours' incubation a distinct blackening of lead acetate occurs in tubes sown with *Br. abortus*, while *Br. melitensis* produces no H_2S at all. On serological grounds, by means of the absorption of agglutinin method, the bovine and porcine *abortus* types may be differentiated from the *melitensis* type.

Br. abortus from cattle is grown best by seeding glycerin-agar slopes with the uterine exudate, and insulating them under a lowered pressure of oxygen or in an atmosphere of 10-per-cent. CO_2. The best method of ascertaining the presence of *Br. abortus* in milk is by the cultural method. The milk is seeded with a liver extract peptone-agar containing 1 : 10,000 gentian violet in a CO_2 atmosphere. Alternatively, 0·5 c.c. of the milk may be injected subcutaneously into the hind leg of a guinea-pig, and the animal killed after three or four weeks ; at the post-mortem the inguinal and lumbar lymph glands will be slightly enlarged and congested.

For isolation of *Br. abortus* from human blood, urine or fæces, the optimum or culture is a medium of pH 6·8, a temperature of 37° C., and an atmosphere of CO_2. When first isolated from the blood or the spleen, the organism may fail to show visible growth on the plates until after three days. Minute dew-drop colonies are then seen, which later become opaque, and are 3 mm. in diameter on the tenth day. Evans considers that 1 per cent. of glucose greatly enhances the vigour of the growth and that the new growth is obtained when liver is substituted for ordinary infusion-agar. For the first few generations of culture an atmosphere of carbon dioxide must be maintained, though this is unnecessary for later generations. Huddleston and Abell have shown

that the growth of *Br. abortus* is inhibited by gentian violet, and that this can be used as a means of differentiation from *Br. melitensis*.

When cultivated from the blood the growth may be exceedingly slow. In one of the Editor's cases Wilson succeeded in demonstrating a growth on the twenty-first day of incubation, and Rainsforth (1933) has recorded success after 60 days.

The isolation of *Br. abortus* from the fæces is no easy matter. Amoss and Poston have succeeded by employing the following technique: a stool suspension is heated with an immune serum and clumps any organisms present in the sediment, which is then seeded into Teague's medium. Two plates are incubated in an atmosphere of air and two in a CO_2 atmosphere.

Br. abortus in cattle. This organism produces abortion in otherwise healthy cows by causing inflammation of the uterine mucous membranes, of the fœtal membranes, and of the fœtus itself. The infection has become very prevalent in highly bred cattle herds when stable fed, both in England and in the United States.

The organisms occur first in the vaginal discharges as well as in the exudate from the uterus, while they are excreted in the milk of infected cows for many weeks and even months, so that *Br. abortus* is frequently found in commercial milk. In Washington 14 per cent. has been found infected, in Chicago 30 per cent., and in Dresden 32 per cent. When injected into guinea-pigs the infected milk produced small tubercle-like foci in the lungs, liver, and kidneys, and swelling of the spleen, which takes about seven weeks to develop. Sheep and pigs are less susceptible than are cows. The symptoms of the affected cow are the escape of varying amounts of greyish-brown mucous discharge from the mucous membranes of the uterus and the chorion. It also affects the udders and probably spreads *via* the lymphatic channels. When a pregnant cow is infected the fœtus is expelled within eight to fourteen days. The fœtus itself shows infiltration of the subcutaneous and intramuscular tissues with *Br. abortus*; the calves are born covered with a purulent exudate and the chorion is converted into a leather-like substance, with buckling and wrinkling of the intercotyledonous parts of the membrane.

Apparently the bull may play an active part in conveying the infection, for the organisms have been found repeatedly in its genital organs.

The commonest time for abortion to be produced in cattle is from the fifth to the seventh month and the incubation period lasts from one to thirty-three weeks.

When introduced into a fresh herd the disease usually spreads rapidly and assumes epidemic proportions; then it passes into an endemic state in which it remains for years. As a rule, the uterus frees itself quickly from the infection and *Br. abortus* is to be found in the udder, and in the supra-mammary and pelvic lymph glands, where it persists. From the udder the organism is excreted into the milk, and so it comes about that 34 per cent. of cows which give a positive agglutination reaction excrete *Br. abortus* in the milk, and it has been proved that they continue to appear there for three years.

Under experimental conditions abortion may be produced in goats, guinea-pigs, rabbits, rats, and mice, and only rarely does it prove fatal. Guinea-pigs may be infected by rubbing cultures on to the depilated skin of the abdomen, and when these animals are infected artificially in this manner, they develop lesions simulating tuberculosis.

Diagnosis.—*Epidemic abortion in cattle.*—The diagnosis of this infection

in cows is made by serum agglutination, which takes place in a titre of 1 : 100 to 1 : 10,000, and the agglutinins can also be proved to be present in the milk of infected cows. For this purpose Bevan has introduced the " abortoscope," which consists of a tube containing a standardized suspension of *Br. abortus*, closed by a cork to which is attached a double loop of thin wire coated with sterile paraffin. On the back of the tube is pasted a label marked " infected." Before use the suspension is thoroughly shaken up, and one loopful of blood from the animal to be tested is taken up in the wire, and on the latter being returned to the tube it is thoroughly shaken to mix the blood with the suspension. The apparatus is then stood upright at room temperature so that in infected cases the suspension and the blood-cells settle down to the bottom of the tube, leaving a clear supernatant fluid through which the word " infected " can be read.

Generally speaking, in cows no attention is paid to an agglutination of a titre less than 1 : 50 in cows' serum. In a pregnant infected animal the titre gradually rises before abortion from 1 : 200 to 1 : 1,000, while a persistent infection of 1 : 400 or over is indicative of an udder infection.

The intradermal test or the abortin reaction in cattle.—This test, on the same lines as the tuberculin, was introduced by MacFaydean and Stockman in 1909 in an attempt to introduce one based upon the hypersensitiveness of infected cows. Holtun (1928) has described a double intradermal test in which 0·2 c.c. of a 5-per-cent. phenolized suspension of *Br. abortus* heated to 65° C. for thirty minutes is twice inoculated into the same site at an interval of forty-eight hours, when the maximum infiltration of the skin is attained forty-eight hours after the injection.

Abortus Infection in Man

Diagnosis.—The agglutination test in abortus infections is much the same as in *melitensis*. An agglutination of 1 : 10 to 1 : 80 in the absence of clinical symptoms indicates a past infection, while a titre of 1 : 100 or over, in the absence of clinical symptoms, probably indicates a latent infection, and a titre of 1 : 100, or over, in the presence of pyrexia and other symptoms of disease, may be considered as diagnostic of an active infection with *Br. abortus*.

The Editor has seen one case which showed a titre of 1 : 10,000, and other typical ones with a titre which never rose above 1 : 80. The agglutination test is best performed by the macroscopic method. A practical method of making a diagnosis by the agglutination test is by means of the " glutoscope," an apparatus devised by Bevan on the same lines as the abortoscope.

The intradermal test, or " *abortin* " reaction, is as useful in the diagnosis of *abortus* infection in man as it is in the *melitensis* infections, and is performed in the same manner (*see* p. 316).

Diagnosis by blood-culture is the same as for *Br. melitensis*, and is successful in about 16 per cent. of cases ; it has already been referred to on p. 317. A certain amount of diagnostic assistance may be obtained from the leucocyte count. There is usually a slight leucopenia with a relative increase in the lymphocytes. The average in seven cases of *abortus* infection under the Editor's care was leucocytes 6,800, with polymorphonuclears 43 per cent. and lymphocytes 48 per cent.

Symptoms.—Cohen divides abortus fever into five types : (1) The classical undulant form ; (2) the arthritic ; (3) the abdominal ; (4) the genital, of which orchitis is the chief feature ; and (5) the "catarrhal jaundice" type. It is doubtful whether there are any signs or symptoms sufficiently obvious to enable a differential diagnosis between *abortus* and *melitensis* to be made from the clinical aspect of the case.

On the whole, *abortus* infections in man run a much milder and shorter course than those of goat-borne *melitensis* infections. Some cases may be so mild that no obvious clinical signs are produced at all beyond the characteristic pyrexia. As a general rule, however, prolonged pyrexial cases lasting many months, as in true undulant fever, are not met with. On the other hand *abortus* infections may be remarkably persistent and persist over a period of a year or more, but a continued abortus fever of over three months duration is rare, though cases with multiple rigors and the characteristic undulatory febrile curve have been seen. Some of the most severe clinical infections seen in England have been the result of laboratory contracted infections.

The spleen may be distinctly palpable as in *melitensis* infections, but is by no means invariably so. The premonitory signs of abortus fever are important ; the infection may commence with pain behind the eyes and in the alveolar margins of the mouth. Unilateral or bilateral orchitis has been noted. There is usually an initial rigor which is followed by headaches, profuse sweats, and arthritic pains.

Hæmorrhage is a somewhat unusual feature. It was noted in 5 per cent. of cases collected by Dalrymple-Champneys. Epistaxis was the commonest manifestation, but melæna, hæmoptysis, hæmatemesis, hæmaturia, menorrhagia, and bleeding from the gums may occur. Robinson (1938) has reported a case in which continuous oozing from the mouth and gums, associated with purpura, almost proved fatal.

Jaundice.—A form resembling epidemic jaundice has been described.

Localizing symptoms.—Usually the arthritic pain and periarthritic effusions which are so characteristic a feature of *melitensis* infections are not so prominent in this type. It is, however, necessary to refer to two instances of isolated joint affections which the Editor has seen. In both these cases the shoulder-joint was affected, apparently due to localized *abortus* infection. Localized abscesses and even fixation abscesses in bone due to *Br. abortus* have been reported, and constitute "surgical brucellosis," as described by Edwards (1937). In Iowa, U.S.A., osteo-myelitis of long bones, including those of the wrist, has been described. Mild or masked cases of *abortus* infection are also met with. In these ascertainable physical signs are absent, but small rises to 99° and 100° F. are seen to occur when a four-hourly chart is kept, and usually only a low-grade agglutination with *abortus* in a titre of 1 : 20 can be demonstrated in these cases. There may be remarkably few symptoms, except, perhaps, headache.

Treatment.—*The treatment of abortus infections does not differ materially from that of the classical disease. As a rule the symptoms are not so urgent and the span of the disease is shorter, so that drastic remedies are not usually called for.*

The cutting short of the fever by protein-shock fever-therapy has been found to be effective by Dr. S. Miller (Harrogate). He has shown that a fever of several months duration can be terminated in a few days by three, or even four, intravenous injections of typhoid-paratyphoid organisms, in doses ranging from 50–150,000,000. The Editor also has treated with success three cases, the fever being cut short by a protein-shock rigor two days subsequent to the isolation of the bacillus from the blood-stream. This may be profitably combined with sulphanilamides.

Fouadin has been tried, as in *Br. melitensis* infections, but the results have not been very striking (*see* p. 320).

Treatment by *sulphanilamides* has been extensively tried out, and rests upon the experimental evidence of Wilson and Maier. They found that these compounds did effectually extirpate the organisms (*Br. abortus*) in experimentally-infected guinea-pigs when administered in large and almost sublethal dosage for some weeks. A summary of the results obtained up to November, 1938, in 13 cases from various sources (French, English and German), shows that the fever defervesced on an average in 15 days from the commencement of sulphanilamide treatment, and that these drugs were exhibited for a period of 17 days. Gaffney considers that, even when cases relapse, as they frequently do, on cessation of sulphanilamide medication, the febrile remission will be of short duration if this treatment is again persisted in. The drug has a definite influence in decreasing the length of the disease. Thomson (1938) has found that *abortus*-infected patients can tolerate *prontosil album* up to 3 grm. daily. Hoerlein (1937), in his summary of the action of these drugs, announced that diseptal compounds exert a favourable influence on *Br. abortus*. Bethoux, Gourdon and Rochedix describe the successful treatment of one intractable case with intravenous injections of 20 c.c. of a 6-per-cent. solution of soluseptasin.

The Editor has treated a series of three persisting and intractable cases in this manner. Two were cases of prolonged fever, the third of pyrexia associated with orchitis. On the whole, he is of the opinion that the more manifest signs and symptoms of this infection are modified by sulphanilamide. He gave prontosil album in doses of 1·5 grm. daily, reinforced by injections of prontosil rubrum 5 c.c. daily, for six days. It is apparently necessary in some cases to inject the drug intramuscularly as well as to administer it by the mouth in order to obtain the necessary concentration.

Prophylaxis.—The prophylaxis of *abortus* infection in man is mainly wrapt up in the very difficult subject of the treatment and prevention of this disease in cattle, for the infection is undoubtedly contracted by the drinking of infected cows' milk by an individual susceptible to the disease. In herds of dairy cows, many carriers of

the infection exist. Prophylactic inoculation and immunization of cattle by employing live cultures of *Br. abortus* has been extensively practised, and the inoculated cows thereupon become passive carriers of the disease, and it is to the introduction of this measure in Denmark and in England that the present prevalence of undulant fever may be ascribed. In 1906 Bang reported that a certain amount of protection could be conferred upon animals by the intravenous injection of living cultures of *Br. abortus* some weeks before copulation, and this method has been more extensively applied by Stockman in 1914 to non-pregnant cattle. It is obvious that the remedy lies in the sterilization of *abortus*-infected milk, and this can be done by boiling or by pasteurization: thirty minutes at 140–145° F. will destroy the organism.

Since it has been reported by Gilbert and Coleman that in 11 cases of human infection in Iowa the source has been traced to association with infected hogs, prophylactic measures have been taken in America in that direction.

CHAPTER XV

ENTERIC FEVERS
(AND BACILLUS COLI INFECTIONS)

THE enteric group of fevers includes typhoid fever, due to *Bacillus (Salmonella) typhosus*, and the paratyphoid fevers, due mainly to *B. paratyphosus-A* and *B. paratyphosus-B*. Paratyphoid-C fever has a somewhat different symptomatology (*see* p. 337). These organisms belong to what is now known as the *Salmonella* group, and the fevers caused by them were known during the Great War as the "enterica" group.

History.—In the earlier half of the nineteenth century, typhoid and typhus fever were grouped together under the term "continued fever." The first clear differentiation of typhoid from typhus on clinical and pathological grounds resulted from the work of Murchison and Jenner (1855–62). Then came the discovery of the *Bacillus typhosus* by Eberth in 1881, followed by that of *B. paratyphosus-A* (Brion and Kayser), of *B. paratyphosus-B* (Schottmüller), and of *B. paratyphosus-C* (Hirschfeld, 1919).

Geographical distribution.—Besides being the scourge of the young European in India, enteric is common enough in Japan, in China, in Cochin-China, in the Philippines, in Malaya, in Mauritius, in West and South Africa, in Algeria, and, in fact, wherever it has been properly looked for. Thanks to protective inoculation with the triple vaccine (T.A.B.) and to sanitary measures, enteric fever during the Great War was no longer the chief disease in our armies.

Prevalence.—Enteric fever was prevalent among young soldiers and recently-arrived civilians in the East, but, fortunately, liability to infection decreases with length of residence, due apparently to a kind of acclimatization. The well-known immunity of native races to typhoid is probably due either to mild attacks of the disease in childhood or to the immunizing effect of living in constant contact with typhoid infection. In insanitary native cities—Chinese, for example—where the European would almost surely contract typhoid, the natives have acquired a high degree of immunity. The typhoid and paratyphoid infections among Europeans in the tropics appear to be more virulent, and to cause a death-rate twice as heavy as that commonly observed in England. According to English statistics, the death-rate is given as about 1 : 8 attacked, but in India only recently the death-rate is stated as rather over 1 : 3.

Up to the early days of this century, typhoid in India used to kill more European soldiers than did cholera. Enteric fevers are

apt to occur in camps in localities previously unoccupied by man. This has long been noted in India, while in Australia typhoid has occurred in the back country many hundreds of miles from human habitations. These observations have suggested that the bacillus may exist as a virulent saprophyte under certain conditions of soil and temperature.

Epidemiology and endemiology.—Practically the essential factor in the propagation of enteric fevers in the tropics, as in temperate climates, is the individual who is passing enteric bacilli in his urine or fæces, or in both. He may be in the acute or the convalescent stage, or a "carrier." Three kinds of enteric carriers are alluded to by writers on this subject: (*a*) The *acute carrier*, who passes enteric bacilli in the excreta for a short period after an attack of enteric fever. (*b*) The *chronic carrier*, who continues to pass enteric bacilli in the excreta for years, possibly permanently. Chronic carriers are more often women than men. The gall-bladder being the seat of a chronic infection, the carrier sometimes suffers from gall-stones and cholecystitis. (*c*) It is believed by some that a person may pass enteric bacilli in the excreta without having at any time previously suffered from an attack of enteric fever. Such a person is called a *passive carrier*.

The enteric carrier is a danger to the community, the degree of danger depending to some extent on his personal hygiene, but much more on the sanitary condition of the locality. Under an efficient water-carriage system of sewage disposal there is a minimum risk of the carrier conveying infection. Where the conservancy system—i.e. the dry closet is employed, as in the tropics generally, the risk of infection is great. The modes of infection are: (1) directly from the infected person (patient or carrier) to the susceptible; (2) indirectly through water supply; and (3) indirectly by fly-carriage and contamination of food.

B. typhosus is practically world-wide in its distribution. Paratyphoid-A fever is the most common form of the infection in the East (India, etc.), paratyphoid-B fever in Europe. During the Great War the majority of enteric infections in France were paratyphoid-B, and the most extensive enteric epidemic occurring in the British and French troops was on the Gallipoli peninsula in 1915. But, relatively to what had happened in former campaigns, the cases of typhoid in this epidemic were few, the armies being almost completely protected by antityphoid inoculation. In the earlier part paratyphoid-B was the prevailing infection, while in the later phases the cases were almost exclusively paratyphoid-A. Paratyphoid-C fever, which is probably identical with the fever caused by *B. aertrycke*, is widespread in British Guiana, but elsewhere has probably not the epidemiological importance of the other three (Giglioli).

Ætiology.—*Description of organisms.*—*B.* (*Salmonella*) *typhosus* is a Gram-negative motile rod, 2–4 μ in length and 0·5 μ in thickness. It is

provided with numerous peritrichous flagella, and is very active when grown on artificial media. On these it thrives well, with growth resembling that of *Bacillus coli*, but less dense. In its biochemical reactions it differs considerably from that organism, and produces acid without gas-formation in maltose, glucose, and mannite, but causes no change in lactose, saccharose, and dulcite. It produces slight acidity in milk without clotting. No indol is produced in peptone water (*see* Table, p. 499). The paratyphoid bacilli A, B, and C resemble in their general morphological characters and staining reactions *B. typhosus*, but differ from it in their biochemical and immunity reactions. They also, like *B. typhosus*, are non-lactose-fermentors, but produce acid and gas in glucose, mannite, maltose, and dulcite, though they do not affect saccharose nor form indol in peptone water. The "A" bacillus is weaker in fermentative power than "B," and it produces permanent acidity in litmus milk, whilst "B" first produces acid, returning later to a permanent alkaline reaction. Their immunity reactions are also quite specific. The "C" bacillus differs from "B" solely in its immunity reactions, and some bacteriologists might prefer to call it a serological race of "B."

The portal of entry of the enteric bacilli into the tissues of their host would appear to be the lymphoid masses forming the Peyer's patches and solitary follicles of the ileum. Here they cause a hyperplasia of the lymphoid tissues, followed at a later stage, in severe cases, by necrosis, sloughing, and ulceration. The bacilli pass on to the lymphatic glands of the mesentery and posterior abdomen, which become enlarged. Finally they enter the blood-stream. The period of bacillæmia coincides with the early febrile stage of the disease, and appropriate hæmoculture is successful in the majority of cases in which it is undertaken sufficiently early—i.e. while the temperature is still rising, or when it is continued without marked remissions. It is seldom successful after the first marked morning remission, especially in paratyphoid fever, or after lysis has commenced. The duration of bacillæmia varies greatly, depending on the severity of the case and duration of the pyrexia. It is, on an average, longer in typhoid than in the paratyphoid fevers. It is important, therefore, in the diagnosis of enteric fever, to set about hæmoculture as early as possible; every day's delay diminishes the chance of success.

It has been suggested that in enteric infections the invading organisms enter the blood-stream first (possibly through the tonsils), and that the intestinal lesions are secondary to the bacillæmia.

Although bacilli are eliminated in the fæces and urine, it is only in a small proportion of cases that they can be isolated from the excreta, even on repeated examinations.

Pathology.—The most striking lesions found post mortem (in addition to the tissue changes common to all continued fevers) are:

Ulceration of the intestine, especially the Peyer's patches and solitary follicles in the ileum and jejunum; enlargement and congestion of the abdominal lymphatics; and enlargement and congestion of the spleen.

The most notable differences in the post-mortem appearances between typhoid and the paratyphoid fever are:

In paratyphoid fevers the intestines more frequently show no change; in paratyphoid fevers the intestines may be acutely inflamed throughout their length, the lymphatic tissue escaping; and in paratyphoid fevers ulceration of the *large* intestine is relatively more frequent. Paratyphoid-C

is in many instances a pure septicæmia, and deep metastatic abscesses due to this organism have been described by Giglioli.

Post-mortem bacteriology.—The causative organism in enteric fevers may be recovered post mortem from the intestinal lesions, the enlarged abdominal lymphatics, the spleen, the gall-bladder, the heart's blood, and other tissues of the body.

Symptoms.—The usual *incubation period* for all the enteric infections is about fourteen days, but it may be shorter than seven or longer than twenty-one days.

There is a wide range in the severity of the infections, and it will be readily understood that one clinical description cannot apply equally to all cases, from the mildest to the most severe. Moreover, the variation is more in the degree than in the nature of the clinical manifestations. After all that has been written, especially during the Great War, on "atypical" enteric fever, this group remains, whether in inoculated or uninoculated patients, remarkably true to one type—which may be termed the "enteric type."

The typical *onset* is a gradual one, but it may, especially in paratyphoid fever, be sudden, with a shiver or even a rigor. Headache is the most constant early symptom, and is usually accompanied by malaise, anorexia, pains throughout the body and limbs, and insomnia. The tongue is coated, the mouth dry and uncomfortable, and the patient thirsty. There is a characteristic moist facies with cheek-flush, and a general apathy. These symptoms vary greatly, and in the mildest cases may pass undetected. Epistaxis is more common in typhoid than in paratyphoid. There may be pain or general uneasiness in the abdomen, but in mild paratyphoids the patient in many cases does not refer to that region. There may be diarrhœa from the commencement, or diarrhœa followed in a few days by constipation, or the patient may have obstinate constipation from the beginning. The temperature is invariably raised. It may mount stepladder-like during the first week, or it may rise suddenly, to reach its highest point in the first 24–28 hours, and, after a period of continued fever, begin to remit in the morning and terminate by lysis. A highly characteristic feature of all the enteric infections is the pulse, which is usually soft, often dicrotic, and relatively slow (Charts 15–17).

On physical examination, the abdomen may be found to be more or less distended, as in severe typhoid, or there may be little or no distension, as in the majority of paratyphoids. Splenic enlargement is practically a constant feature, the organ usually enlarging sufficiently to render, at some stages of the illness, its lower pole palpable below the left costal margin. It may be felt in some cases on the second or third day, if the patient comes under observation so early, or it may not be palpable till the second or third week, or even later. In some cases it becomes palpable for the first time only after the temperature has become normal. Usually about the seventh to the tenth day, but it may be earlier or much later, "rose spots" appear. These

vary considerably in number, size, shape, general characters, and distribution. There may be only two or three on the abdomen, or the body and limbs may be covered, from the soles of the feet to the

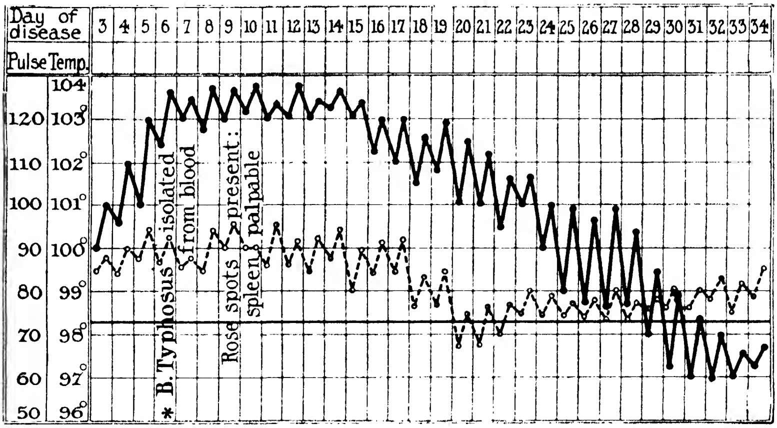


Chart 15.—Typhoid fever, with graph of pulse-rate. (*Garrow.*)

scalp. They are of a pale-rose colour, slightly raised, round or lenticular, and fade on pressure. The more profuse eruptions occur in paratyphoid fever, especially paratyphoid-A. When the eruption is not of this profuse type its distribution is characteristic: 90 per cent

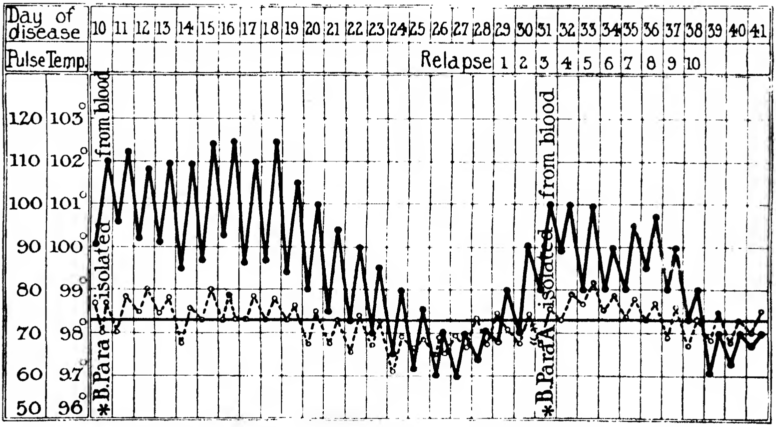


Chart 16.—Paratyphoid-A fever, with graph of pulse-rate. (*Garrow.*)

or more of it is on the trunk, between the levels of the iliac crests and the nipples. The patient usually coughs and has a certain degree of bronchitis.

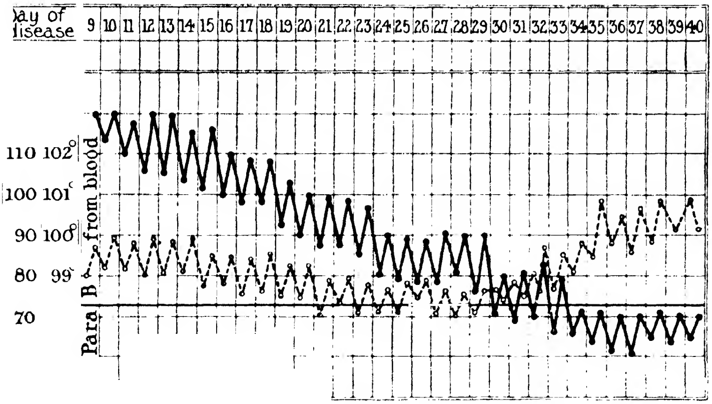


Chart 17.—Paratyphoid-B fever, with graph of pulse-rate. (*Garrow.*)

Diagnosis

Clinical diagnosis.—In the literature of enteric there is frequent reference to mild, atypical, abortive, and clinically unrecognizable forms; and it appears to have become the custom to leave the question of diagnosis to the laboratory. This was particularly so during the Great War, both at home and abroad, and it is greatly to be deprecated, because careful and repeated clinical scrutiny of these cases is more than ever necessary. It is Garrow's opinion that the great majority can be correctly diagnosed clinically. While laboratory methods of diagnosis in the enteric group are undoubtedly important, undue value has been attached to certain bacteriological and serological findings, even to the extent of creating new clinical types of the disease to correspond to them. Far from being protean in their clinical manifestations, the enteric fevers are remarkably constant and true to type. The cardinal signs are five in number:

(1) Pyrexia of remittent type ending by lysis; (2) low pulse-temperature ratio; (3) characteristic toxæmia; (4) splenic enlargement; (5) eruption of rose spots. It is not pretended that this list exhausts the diagnostic signs and symptoms; but a consideration of these five signs will, in the great majority even of the milder cases, lead to correct diagnosis.

(1) *Pyrexia.*—Continued pyrexia of remittent type, ending by lysis, may be regarded as a feature of every case of acute enteric fever (typhoid or paratyphoid). The pyrexia may be high or low, long or short, with remissions great or small. The onset of pyrexia may be gradual or sudden, and lysis may be slow or rapid, thus giving a great variety of temperature charts within the type; but there is no good evidence to show that the fever ever departs from this type.

Cases presenting the following features certainly should not be regarded as enteric:

(*a*) Temperature is normal or subnormal throughout the entire illness ("apyrexial type of enteric").
(*b*) Temperature reaches normal or subnormal at some period of the twenty-four hours on every day of the illness ("intermittent type of enteric").
(*c*) Temperature shows perfect tertian or quartan periodicity throughout ("malarial type of enteric").
(*d*) Temperature shows a series of short relapses of one to three days' duration, occurring at intervals of a few days ("trench-fever type of enteric").
(*e*) The temperature ends by a genuine crisis.

Examples of all these so-called "types of enteric fever" will be found in the literature, the erroneous diagnosis having been based upon the unwarrantable bacteriological or serological finding.

(2) *Low pulse-temperature ratio.*—One of the most valuable diagnostic points is the slowness of the pulse in relation to the pyrexia. The normal pulse-temperature ratio may be tabulated as follows:

Pulse . .	50	60	70	80	90	100	110	120	130	140
Temperature .	96°	97°	98°	99°	100°	101°	102	103°	104°	105°

In enteric fever the pulse is, as a rule, 20 or 30 or 40 beats per minute slower than thus indicated. For example, it is common to find an enteric patient with a temperature ranging about 103° to 104° F., and a pulse of 90 beats per minute, or it may be even slower. If the pulse is recorded graphically in red ink alongside the temperature curve in black, a very striking clinical feature of great diagnostic significance is clearly brought out.

(3) *Characteristic toxæmia.*—There is something very characteristic in the general appearance, facies, and decubitus of the enteric-fever patient. The disease may in many cases be confidently diagnosed by a glance at him as he lies in bed. He has a dull, heavy, toxin-laden appearance in the early acute stage of his disease, with a moist face and flushed cheeks. The experienced clinician at once recognizes the difference between this and the toxæmia of, say, malaria or relapsing fever. In the mildest paratyphoid infections there is little or nothing of this toxic appearance, whilst some infections other than enteric are accompanied by a general toxæmia closely resembling it. Nevertheless, this sign, to the experienced physician, when taken in conjunction with the others, is of diagnostic significance.

(4) *Splenic enlargement.*—As some degree of splenomegaly is practically an invariable feature of enteric fever, this sign is of considerable value in making a diagnosis. Unlike the majority of tropical splenomegalies from other causes (malaria, kala-azar, etc.), the enlargement is acute, so that, even when superadded to a spleen

already enlarged from malaria, it has certain exceptional features of diagnostic significance. For example, the acutely enlarged spleen of enteric is tender. On palpation, the edge is seldom more than two fingers' breadth below the costal margin, often not so much ; and the enlargement is of comparatively short duration. The spleen may only be palpable for two or three days, and then recede. It may become palpable as early as the second or third day of fever, or not till the second or third week, and it may remain enlarged long into convalescence.

(5) *Rose spots* may appear in the first week, but more often in the second, and tend to come in crops. They may not appear till the temperature is normal. In warm climates, many European skins are apt to show spots more or less like those of enteric fever, as the result of mosquito-bites and of inflammation of hair follicles, sweat-glands, etc. Great care must be taken in discriminating between the true spot and these "pseudo-rose spots." There are many European skins which, in spite of the trying conditions of the tropics, remain free from blemishes of this sort, and in these cases the recognition of the typical spots is relatively easy.

Summary of clinical diagnosis.—Every undiagnosed fever in the tropics should be regarded as a possible case of enteric fever and closely observed clinically, at the same time that bacteriological and serological investigations are being carried out and Marris's atropine test is applied. While valuable clinical evidence may be obtained from occasional signs, such as epistaxis, pea-soup stools, abdominal distension, and hæmorrhage from the bowel, the diagnosis should rest in the great majority of cases upon the presence or absence of the five cardinal signs above described. Any case presenting the first, second, and third signs should be treated as enteric (whether the diagnosis is supported by laboratory findings or not) until some other definite diagnosis is arrived at. No case which does not show the first, together with at least two of the remaining four cardinal signs, should be definitely regarded as such. Five types of temperature chart have been described, any of which excludes enteric. These, however, imply that the case has had its temperature recorded from the first, which is not often possible. In the majority of cases of active enteric fever, all five signs are presented at one or other stage of the illness.

Finally, it should be remembered that, for every case of enteric fever which imitates some other disease, there are at least a score of cases of other diseases imitating enteric (malaria, trench fever, phthisis, liver abscess, syphilis, etc.).

Paratyphoid-C.—Some space must be devoted to paratyphoid-C fever as observed by Giglioli in British Guiana. Although essentially a "fever" producing a temperature chart not unlike those of other paratyphoid fevers, yet it is essentially a septicæmia and the intestinal tract is not specially involved. Complications in the form of arthritis, abscess formation, and cholecystitis are common, and fixation abscesses

due to intramuscular quinine injections may contain a pure culture of this organism. There appears to be a special connection between paratyphoid-C infection and malaria. The mortality of a series of 92 cases of definitely diagnosed paratyphoid-C infections was 38 per cent. Probably a great number of abortive and mild cases passed unobserved.

Bacteriological diagnosis of "enteric" (*see* p. 1036).—(*a*) *Hæmoculture* is unquestionably the most satisfactory method of diagnosis; it should be employed, wherever the necessary facilities are available, in every case of undiagnosed pyrexia in the tropics so soon as a blood-film is found to be free from malaria parasites. A successful hæmoculture furnishes the only conclusive evidence that the patient is suffering from active enteric fever, and can hardly be said to be open to fallacy. Unfortunately, however, the usefulness of the method is limited by the short duration of bacillæmia. In many cases which are undoubtedly enteric, negative results are obtained because hæmoculture has been attempted too late. Recent experience has shown that culture from the *blood-clot* gives the highest percentage of positive results.

(*b*) *Culture of excreta.*—The plating of urine and stools should be undertaken when blood-culture has failed, and should be repeated during convalescence to determine whether the patient is free from infection. Bacilluria occurs generally after the fourteenth day, and in about 15–20 per cent. of the cases, and, under modern conditions, employing brilliant green and Endo's medium, cultivation of the organisms from the fæces in all stages is much more successful as a diagnostic measure than formerly has been the case. Some positive findings from culture of excreta are open to fallacy. The case may be one of an enteric carrier suffering from some illness other than enteric —e.g., malaria or trench fever. The detection of carriers can only be effectually carried out in a fully-equipped laboratory; at least seven separate and consecutive bacteriological fæcal tests are necessary.

Serological diagnosis.—One of the simplest and most reliable of laboratory tests is the examination of the blood-serum of suspected enteric-fever patients for the specific agglutinins of the enteric bacilli—the *Widal reaction.* When carefully applied by reliable methods in the case of *uninoculated patients,* it leads to a correct diagnosis in the great majority of cases. Assuming correct technique, the only possible fallacies are that a positive Widal reaction may result from a *previous* attack of enteric, and that a negative result may occur in the early stage of an attack of enteric. If a negative finding is obtained in face of clinical data pointing to enteric, the test should be repeated, on several occasions if necessary. A few cases of enteric, especially paratyphoid-A, may fail to develop agglutinins and continue to give a misleading negative Widal reaction throughout.

The serological diagnosis of the enteric fevers in *inoculated patients* gave rise to much conflict of opinion during the Great War. Inoculation produced in the blood-serum specific agglutinins indistinguishable qualitatively or quantitatively from those produced by infection. The mere recognition of these specific substances, therefore, had not the diagnostic significance in the inoculated that it has in the uninoculated. It had, until the recognition

of H. and O. agglutinins, hardly any diagnostic value. It was demonstrated however, by Dreyer and his co-workers, and by others, that if an accurate estimate of the agglutinin content of the serum is made early in enteric fever and repeated at intervals of a few days, there is a steady rise to a maximum, followed by a slower fall. Dreyer and Walker stated that this maximum usually occurred between the eighteenth and twenty-first day of the illness, and almost invariably between the sixteenth and twenty-fourth day. They therefore gave to the latter period the name "period of expectation." To this agglutinin fluctuation they attached a significance practically pathognomonic. The agglutinin fluctuation, when considered in relation to the clinical data, though useful, cannot now in itself be regarded as conclusive (*see* p. 1039).

In uninoculated patients differential diagnosis is obtained by carrying out agglutination tests with the patient's blood-serum against emulsions of the four organisms concerned. Each infection produces its specific agglutinin, and the phenomenon of coagglutination does not often interfere with the diagnosis. In patients who have been inoculated with triple vaccine the problem of differential diagnosis is considerably complicated. The response may be specific, but frequently two or all three agglutinins may show variations (*see* Appendix, p. 1037). It is still held, as stated above, that a progressive rise in agglutinin titre to one specific antigen denotes active infection ; but it must be stressed that a rise in immune bodies (or residual-amanestic agglutinins) may be stimulated by other pyrogenic infections, such as malaria.

It is almost impossible in a manual of this description to follow accurately all the investigations on the antigenic value of the serum and of the different variations in the antigens themselves which have been undertaken by modern workers. Felix and Pitt have shown that strains of *B. typhosus* of high virulence have the property of being relatively inagglutinable by sera which contain a high titre of antibody acting on the "O" somatic antigen, which is one of the most characteristic components of the "smooth" strains, and this inagglutinability is associated with the possession of additional antigenic constituents which can be differentiated from the ordinary "O" antigen. Thus mice immunized with a vaccine containing the additional antigen in an active form are rendered resistant to injection of highly virulent bacilli. This antigen is separate and distinct from the "O" and "H (flagellar)" antigens of *B. typhosus* (and apparently this applies to the paratyphoid group) and renders the "O" antigen resistant to the "O" antibody. The symbol V_1 (referring to virulence) is suggested for this antigen and the corresponding antibody. This V_1 antibody is demonstrable by agglutination and absorption tests, and its *in vitro* titre is comparatively low. Active and passive immunization disclose the powerful protective action of the V_1 antibody. The "O" antibody also neutralizes the *endotoxin* of *B. typhosus*, whereas the V_1 and "H" antibodies are incapable of this action. Perry, Findlay and Bensted have now shown that virulence for mice rather than mere smoothness in the usually accepted sense offers the best criterion of the immunizing power.

The symbols "H" and "O" stand for German terms which denote respectively cultures which spread or which remain circumscribed. There are two main types of *typhoid bacilli:* the V form which contains "H,"

" O " and V_1 antigens, and the " W " form which does not contain V_1 antigen. Craigie has now discovered a method of typing typhoid bacilli by specific bacteriophages, of which no less than 13 are now recognized, and by the use of which it is possible to detect the source from which the organisms have been derived.

The original claim made by Felix that only " H," but not " O " agglutinins are formed as the result of passive inoculation, and not as the result of infection by living organisms, appears to be incorrect, since both may appear, and also V_1 agglutinins, as the result of inoculation with dead organisms. It is held that " H " agglutininogens are heat-labile and are also destroyed by alcohol, while " O " agglutininogens are heat-stable.

Atropine test.—This test, devised by Marris, depends on the fact that in health, or disease other than enteric, a hypodermic injection of atropine sulphate ($\frac{1}{33}$ gr.) is followed by a rise in the pulse-rate amounting to at least 15 beats per minute, whereas in enteric no such rise follows. Should there be any rise at all, it will be less than 14 beats per minute, but often there is none.

In the application of the test the patient should lie horizontally and remain at perfect rest. He should not be tested till at least one hour has elapsed since the last meal. The pulse-rate should be counted for at least ten minutes, and then $\frac{1}{33}$ gr. of atropine should be injected over the triceps region. After an interval of twenty-five minutes the pulse should be counted again, minute by minute, until it is clear that any rise which may have followed the injection has begun to pass off. The period of the disease during which the test is most reliable is said to be the fifth day to the end of the second week.

Auxiliary methods of diagnosis.—The diazo-reaction in the urine is useful, but may be present in malaria. Russo's methylene-blue test is said to be more conclusive, as it is absent in malaria.

Differential diagnosis.—The abdominal pain of enteric may be mistaken for *appendicitis*, but the matter may be easily settled by a leucocyte-count, which in the former is a leucopenia with a relative lymphocytosis, and in the latter an active leucocytosis. *Bacillus coli infections* may resemble enteric. *Typhus* is notably difficult to distinguish in its earlier phases; the leucocytosis which is present in that disease will be found of considerable assistance.

It must not be forgotten that enteric fever may coexist with some other acute infection such as malaria.

Diagnosis of typhoid from paratyphoid.—There are no *clinical* features which serve to distinguish the typhoid and paratyphoid infections from one another with any certainty. Yet there are general points in which they differ. Thus, typhoid fever (*B. typhosus* infection) is the most severe fever of the group, with the highest case-mortality (15 per cent. or over, as compared with 2 per cent. or less for the paratyphoid fevers). The typhoid patient looks more toxic; his temperature is, on an average, higher, with smaller morning remissions; he more frequently shows evidence of gross intestinal lesions (ulceration) e.g. diarrhœa, hæmorrhage, abdominal distension, perforation. The rash is more scanty and the individual " rose spots " are smaller and slightly darker than in paratyphoid. There is greater loss of flesh

in typhoid than in paratyphoid. Paratyphoid is characterized by a milder toxæmia. There is seldom abdominal pain or distension, and constipation is the rule. Hæmorrhage and perforation are rare. The rash is more profuse and may cover the entire body and limbs.

But typhoid is frequently of the very mild type, and, on the other hand, paratyphoid may be like the worst typhoid. It is therefore quite impossible to say on clinical grounds alone whether any individual case is one of typhoid or paratyphoid.

Still less is it possible to arrive at a differential diagnosis on clinical grounds between " A," " B," and " C " cases of paratyphoid, although here again, over a series of cases, distinct clinical differences can be noticed. For example, relapses in paratyphoid-A are more frequent than in any other of the enteric infections, and less frequent in paratyphoid-B. Paratyphoid-A is, on an average, of longer febrile duration than paratyphoid-B, but the latter, on the other hand, is more often followed by jaundice, thrombosis and suppurative complications.

Paratyphoid-C fever is prevalent on the Demerara River, British Guiana. About 92 cases which have been proved bacteriologically have been recorded, so that this disease is probably endemic and a fairly common disease (Giglioli). It produces an irregular type of fever and the character of the signs and symptoms may be rather negative; diagnosis can be determined solely by isolation of the causative organism. A small series of cases are recorded in the Army returns from India during recent years.

Treatment.—There is no generally accepted specific therapy for enteric fever; nor is there any drug which is known to exercise an active influence over this disease. In these circumstances it is best to confine treatment to providing the best hygienic conditions, good nursing, and careful dieting. All that the great majority of mild paratyphoid cases require is a soap-and-water enema every other day to relieve the constipation. Milk should be the diet while the patient is febrile; thereafter custard, milk pudding, soup, fish, and meat diet. The diet should contain about 70 grm. of protein a day, with a caloric value of 2,500–3,000. Water should be given freely. Purgative medicines should be avoided. The care and cleanliness of the mouth and teeth are important.

In cases marked by great toxicity with high temperature (over 102·5° F.) and no morning remissions, tepid sponging is beneficial; in the worst cases the cold bath or ice pack may be resorted to. The temperature of the water should be between 70° and 85° F.; a tub of canvas and mackintosh sheeting may be improvised. Food may be given as a stimulant after the bath. The rectal temperature should be taken immediately on removal from the water, and again three-quarters of an hour later.

Felix's antiserum treatment.—Based upon his observations on the virulence of smooth strains of *B. typhosus* towards the " O " antibody

and the new V_1 antigen which is definitely associated with virulence, Felix (1935) has produced an efficient antiserum from horses by injecting the V antibody. The therapeutic effects of this serum have been tested in a number of cases in Palestine and in Dublin. The results so far obtained are distinctly encouraging, for they indicate a favourable action on the toxæmic manifestations of the disease and the pyrexia. The dose is 25 c.c. of serum on three successive days. In very severe cases this dose may be doubled. McSweeney has reported the recovery of a dangerous case of relapse treated in this manner, as well as of a child of four years with typhoid meningitis in which the bacillus had been recovered from the cerebro-spinal fluid.

It is necessary that the serum should be injected early in the course of the disease. Cookson and Facey (1937), in a report upon 73 cases, noted in 73 per cent. an improvement within forty-eight hours of the injection ; in a further 10 per cent., some benefit accrued after a few days' interval, and in these it is possible that the action of the serum was delayed. The mortality of patients treated in this manner was 9·5 per cent. Robertson and Yu in Shanghai have confirmed these results in 52 severe cases of typhoid. Using a concentrated serum, the standard dose employed for an adult was 50 c.c. administered intramuscularly. Thirty cases responded by a drop in temperature and a decrease in toxic symptoms. In 15 cases no appreciable effects were observed.

Vitamin C in treatment.—Injection of this vitamin by the intravenous route, together with extracts of the suprarenal glands containing the hormone, have been advocated by Hartmann and others. Najib-Farah in Cairo (1938) advocates this line of treatment. The cortical hormone is *Eschatin* (P. D. & Co.), which contains only a negligible quantity of adrenalin. The vitamin C preparation is known as Cébion (Merck). It is considered that these products play a defensive rôle in enteric infections. As soon as the diagnosis is established, the intravenous injection of suprarenal cortical extract is commenced in doses from 5–20 c.c., together with 500–1,000 mgm. of vitamin C. The two products are injected together. No oral medication need be given, but an icebag should be applied to the abdomen. The administration of suprarenal cortex and vitamin C is continued for five to twelve days, and is followed by two intravenous injections daily of 500 mgm. vitamin C for seven days.

The management of convalescence demands care, especially in paratyphoid-A infections, and the return to solid diet should be postponed until the temperature has remained normal for at least ten days.

For the bacilluria associated with enteric, urotropine (hexamine) in doses of 10 gr. three times a day usually acts as a specific, but now the sulphanilamides—M & B 693 especially—are proving more efficacious.

In the event of hæmorrhage, all fluids should be stopped for at least 48 hours, and sufficient morphia injected to keep the patient at rest. Though a very large amount of blood may be lost without

causing a fatal result, yet, when feeding is recommenced it should be proceeded with very carefully. As a general rule, one large hæmorrhage is less serious than a number of smaller ones. When bleeding has ceased, a subcutaneous infusion with saline up to 1½ pints may be permitted, and this may be repeated later should no further hæmorrhage occur. It is advisable, should hæmorrhage be suspected, to give 30 gr. of calcium lactate three times daily; some make a practice of doing so from the sixteenth to the twentieth day of a typhoid fever, and from the fourteenth to the eighteenth day of a paratyphoid. In cases with thrombosis, administration of citrates is indicated.

Prophylaxis.—*Anti-enteric inoculation* is conspicuously successful as shown by the statistics of the American Army, and of the British Army in India. During the Great War the vaccine was modified by the introduction of *B. paratyphosus-A* and *-B*, and the statistics furnish conclusive evidence of the efficacy of this measure of prevention, not only in lessening the incidence, but also in modifying the disease or diseases. Therefore, everybody proceeding from a country such as England to the tropics or subtropics should be inoculated with two doses of triple vaccine (T.A.B.), and should be re-inoculated every three years subsequently with one dose, so long as he remains in a country where enteric is prevalent.

The typhoid vaccine, as originally introduced, caused a considerable reaction, but by better methods of preparation and dosage in recent years the reaction has been mitigated. The official vaccine contains 1,000 millions of typhoid bacilli, 750 millions of paratyphoid-A, and an equal number of paratyphoid-B, to each c.c. Two doses of 0·5 c.c. and 1 c.c. are given at an interval of ten days. The reaction in the majority of instances is very slight. Occasionally, however, cases of persistent pyrexia with severe local symptoms, malaise, and headache are met with. In countries where paratyphoid-C is prevalent a tetravalent vaccine should be employed.

Preparation of the vaccine.—The organisms are grown upon trypsin-agar, washed off in saline and killed by heat. The vaccine is then standardized by combining the various bacterial suspensions in their appropriate proportions. The final emulsion is preserved by the addition of 0·4-per-cent. lysol.

Statistics.—During the South African War, when prophylactic inoculation was incompletely practised, there were 60,000 cases of enteric, with 8,227 deaths. With millions of men under arms during the first two years of the Great War, only some 4,000 cases of enteric were reported from France, with a case-mortality of less than 2 per cent. In the Navy, Bassett-Smith's statistics record an incidence of only 144 cases of enteric during the year 1917, of which 8 occurred in inoculated and 136 in uninoculated individuals.

The American Army shows much the same figures; for two years, 1917–19, out of an average strength of over two million men, there were only 213 deaths from enteric, and it is calculated that had typhoid prevailed in the same proportion as in the uninoculated troops in the Spanish-American War the death-roll from this cause would have been over 60,000.

In the Royal Air Force a dissolved T.A.B. vaccine is used, the solven

being sodium lauryl sulphate. This vaccine is prepared by Glaxo Laboratories. When injected it gives rise to reactions considerably milder than did that formerly employed, though it appears to produce an equal quantity of bactericidal bodies in the blood of inoculated persons. No definite correlation could be found between the H and O agglutinin titre and the bactericidal potency of the human sera tested.

The problem of enteric infections among natives employed in the Rand Gold Mines has given rise to a considerable degree of anxiety. In seven years (1930–37) the number of cases was 6,611, and the "carrier problem" among these people is a very serious one. In December, 1936, inoculation with *endotoxoid* vaccine was initiated, with a great diminution in the number of cases of "enteric" notified. The prophylactic inoculation against typhoid and paratyphoid fevers has been recommended by the Transvaal Mines Medical Officers' Association.

Measures to avoid infection.—The most effective method for avoiding enteric infection is the water-carriage system of sewage-disposal. This, however, is not general in the tropics, so that other methods must be considered. They are: (*a*) detection of enteric carriers and their control, especially in relation to the selection, distribution, and cooking of food; (*b*) protection of water supplies; (*c*) extermination of flies, and preventing them from access to excreta and refuse on the one hand, and to food for human consumption on the other.

Enteric-like Fevers

Septicæmia due to Bacillus fæcalis alkaligenes and other organisms.—During recent years a series of mild pyrexias, of either remittent or intermittent type, has been proved by Hirst and others to be due to infection with *B. fæcalis alkaligenes* (Table, p. 499). It is a common inhabitant of the intestinal canal, where it is not definitely known to exert any pathogenic action. The fever it gives rise to when it is present in the blood-stream may last from two to fifteen days. There is an evening rise with marked morning remission. The symptoms resemble those of a mild enteric, the pulse is slow in relation to the temperature, and the tongue is slightly furred. In some cases the patient's serum clumps the homologous organism in a dilution of 1 in 50.

In outbreaks of food-poisoning or "ptomaine poisoning," which occur from time to time, bacilli of the Salmonella group, *B. enteritidis* and *B. aertrycke* (*suipestifer*), have been isolated from the blood-stream. The fevers they produce have many features in common with enteric. They differ in the suddenness of the onset with rigors, the accentuation of the gastro-intestinal symptoms, the short duration and rapid termination of the fever. *B. aertrycke* resembles *B. paratyphosus-B* in its biochemical, but may be differentiated from it upon its serological reactions.

Bacillus coli infections.—Infection of the bladder and urinary tract with *B. coli* is frequently met with in both sexes in the tropics. Should the organism enter the blood-stream it may give rise to a prolonged intermittent pyrexia resembling enteric. *B. coli* septicæmia and pyæmia may be a terminal infection in debilitated natives, especially after bacillary dysentery; in these cases the organisms gain entrance to the blood-stream through the intestinal lesions, and, becoming arrested in the glomeruli, give rise to multiple minute

abscesses in the cortex of the kidneys, from which they escape in an intermittent manner and appear in the urine (Fig. 45). The condition is probably much more widespread than has been recognized hitherto, and a series of cases from Egypt has been described by Enright and the Editor. The general condition of the patient, the stupor and the intoxication, may resemble

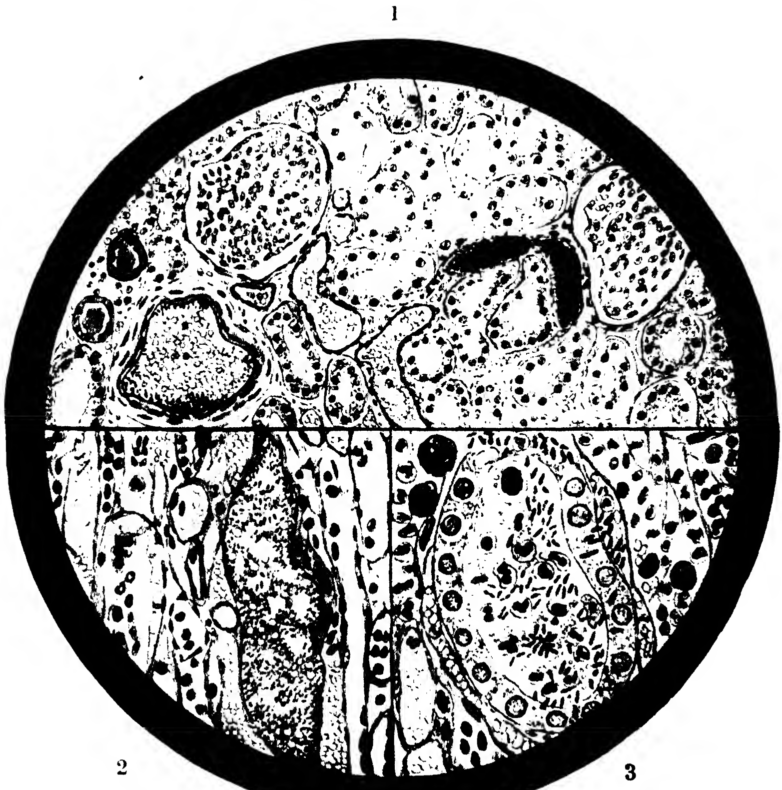


Fig. 45.—Sections of kidney in *B. coli* septicæmia. (*Orig.*)

1, Aggregation of organisms in intertubular capillaries; 2, large collection of organisms in a medullary vein; 3, passage of bacilli through tubular epithelium of duct of Bellini into lumen.

those of enteric, but the onset is generally sudden, with headache, and acute pain referred to both kidney regions. Usually all symptoms of vesical irritation are absent. The tongue is thickly furred; rigors are numerous and accompanied by profuse sweats. The organism may be recovered in pure culture from the blood-stream during the rigors, as well as from the urine by ureteric catheterization. The acute attacks are liable to be confused with those of malaria. This form is apparently susceptible to sulphanilamide treatment.

Pyelitis.—Owing to the propinquity of the renal pelvis to the colon acute pyelitis due to infection with *B. coli* is very apt to occur, especially in women, in the tropics. The symptoms may commence with a rigor and a dull aching pain in the loins which is increased on pressure. Micturition may be frequent and sometimes a large and tender kidney may be palpated. The results of the inflammation are soon seen in the urine, which contains albumin, pus cells and, sometimes, even blood. *Bacillus coli* is present in large numbers especially in the first specimen of urine passed during the day. Differentiation from malaria, an attack of which it may closely resemble, may be necessary. *Cystitis* with pyrexia and acid urine may also be due to *B. coli* and is very apt to occur as a sequel to any debilitating tropical fever, especially in enteric infections. It is always necessary to consider the possibility of this occurrence.

The treatment of *Bacillus-coli* infections of the urinary tract, which is so important in tropical practice, has been placed on a much surer and more satisfactory footing by modern discoveries in therapeutics It was found that the excretion of ketone bodies in the urine destroyed the greater number of the *Bacillus coli* organisms present, and this led to the application of *mandelic acid*, which produces similar changes in the urine. Mandelic acid is related to B-hydroxybutyric acid and produces a high degree of acidity—*p*H 5—in the urine together with acetone. A methyl-red indicator is employed to estimate the hydrogen-ion concentration.

It must be emphasized that, in employing these therapeutic measures, the condition of the kidneys and ureters should first be ascertained by means of excretion urography (uroselectan). Sometimes a calculus may be discovered in the renal pelvis or in the ureters, which may be the seat of the *B. coli* infection, necessitating surgical measures.

The original mandelic acid method has now been superseded by the use of more modern preparations such as ammonium mandelate, mandelix and mandecol, in which ammonium chloride is combined with mandelic acid. These preparations are given as 1–2-drachm doses three times daily directly after meals until the urine has become sufficiently acid, the fluid intake being restricted to 40 oz. daily, and are very often successful in cases of pure *B.-coli* pyelitis.

More recently, however, the sulphanilamides have come into use and threaten to supersede the mandelic acid preparations. They are especially useful in *B.-coli* cystitis and trigonitis. The Editor has employed *prontosil* and *uleron* in doses up to 3 grm. daily for ten to fourteen days. This may be reinforced, if necessary, by after-treatment with mandelic acid preparations. Kenny, Johnston, and von Haebler (1937) recommend *p*-aminobenzene sulphonamide in the treatment of *B.-coli* infections of the urinary tract. This is especially important in the *B.-coli* pyelitis of children, and also in pregnant women. Comparatively small doses (1·5 grm. daily) effect a rapid disappearance of *B. coli* and pus cells and the remission of symptoms. It has been found that the bactericidal power of the urine is roughly proportional to the sulphonamide content. *Prontosil album* appears to be effective in doses of 1·8 grm. daily for seven days. The toxic manifestations of this drug, which include sulphæmoglobinæmia or methæmoglobinæmia, are not commonly seen. In some it may produce headaches, or even drug fever and abdominal pain. While this drug is being exhibited, eggs and other sulphur-containing substances should be eliminated from the diet. It is necessary to estimate the leucocyte count at regular intervals, as a leucopenia, or even agranulocytosis, may be produced.

Subsection E.—DISEASES CAUSED BY VIRUSES

Preliminary Statement

The subject of virus infections is one which is becoming increasingly important since year by year the number of human, animal and plant diseases attributed to the agency of viruses grows greater. The consensus of opinion now inclines to the view that bacteriophages must also be included in the same category.

It is, however, recognized that not all viruses are similar in character. Certain plant viruses, such as those of tobacco mosaic and bushy stunt of tomatoes, and those affecting cucumbers, have been shown by Stanley in America and by workers in Great Britain, to consist of heavy proteins—almost certainly nucleo-proteins—with molecular weights of several millions. Certain of these viruses can be obtained in the form of true crystals. Although there is evidence that bacteriophage and some animal viruses may also be heavy proteins, no animal virus has yet been isolated in a crystalline form. The larger animal viruses, at any rate, are more complex in composition, and a few of them, notably those producing psittacosis, trachoma, inclusion conjunctivitis and lymphogranuloma inguinale, exhibit developmental cycles recalling those described for the rickettsiæ. Unlike rickettsiæ, however, these viruses are not transmitted by arthropods.

Very frequently the adjectives " filterable " or " ultra-microscopic " are applied to viruses : both are unsatisfactory. Many of the smaller bacteria readily pass through filter candles, while the same is true of many spirochætes. Certain bacteria, such as those causing pleuro-pneumonia of cattle, or agalactia in sheep, also have filterable phases, while many true viruses only pass with difficulty through diatomaceous or porcelain filters. With ordinary microscopes, using direct illumination, the limit of resolution lies between 0·1 and 0·2 μ. Barnard, using ultra-violet light and special optical apparatus, has, however, been able to photograph bodies of considerably smaller size. Many of the larger viruses, such as those of psittacosis, vaccinia, ectromelia, and herpes febrilis, have thus been successfully photographed, and stained, the dimensions obtained by these means agreeing very closely with those calculated from filtration experiments. Probably the best working definition of viruses is that suggested by Gardner, who refers to them as " agents below, or on the borderline of microscopical visibility which cause disturbance of the function of living cells and are regenerated in the process."

History.—It is of interest to note that as early as 1728, twenty years before the birth of Jenner and long before bacteria were associated with disease, the term " virus " was applied to the causal agent of smallpox. Pasteur, in the course of his work on rabies, first suggested the possibility of ultra-microscopic organisms. It was only in 1892, however, that as a result of the work of Iwanoski, the juice of tobacco-plants suffering from mosaic disease was found capable of infecting healthy plants after passing

through bacteria-proof filters. In 1897 Loeffler and Frosch found by chance that foot-and-mouth disease could be produced by an "infective principle" which passed through porcelain filters. The infectivity of viruses for animals was thus demonstrated. Since that time more than 100 diseases due to filterable viruses have been discovered affecting man, mammals, birds, amphibians, fish, insects, plants, and, if bacteriophage be included, bacteria.

Diseases caused by viruses.—In the list of infections produced by these agents must be placed mosaic diseases of plants, wilt and polyhedral diseases of insects, fowl-plague, fowl-pox, leukæmia, and filterable tumours of hens, infectious anæmia and Borna disease of horses, louping ill, foot-and-mouth disease, hog cholera, dog distemper, cat distemper, and—of special importance in the tropics—rinderpest of cattle, blue tongue of sheep, Nairobi sheep disease, and African horse sickness. The virus diseases of man which are of special tropical interest include smallpox and alastrim, rabies, yellow fever, dengue, Rift Valley fever, phlebotomus fever, psittacosis, trachoma, lymphogranuloma inguinale, and inclusion conjunctivitis. Many other virus infections are of universal distribution but may be responsible for severe epidemics in tropical countries. The list includes measles, influenza, varicella, rubella, mumps, herpes febrilis and probably herpes zoster, warts, molluscum contagiosum, anterior poliomyelitis, St. Louis encephalitis, Japanese type-B encephalitis, equine encephalo-myelitis, lymphocytic chorio-meningitis, and probably infective hepatitis, encephalitis lethargica and Australian X disease.

The action of viruses on cells.—The only certain method at present available of detecting the presence of viruses is by their pathogenic action on the cells of susceptible animals. It is possible that non-pathogenic free living viruses exist, and there is certainly evidence to show that many viruses may lead to a more or less saphrophytic existence, only becoming pathogenic when inoculated into tissues other than those in which they normally dwell: examples are Virus III infection of rabbits, or salivary-gland disease of guinea-pigs. The virus of herpes febrilis may be found in the saliva of a high percentage of normal persons.

All viruses at present known are closely associated with living cells, and whether *in vivo* or *in vitro* require living cells for their multiplication. The action of viruses on cells is characterized either by stimulation or by depression of cell physiology; in certain instances a primary stimulation is followed by depression. Stimulation is characterized by active multiplication or hypertrophy of the cells, as in infective warts, fowl-pox, Shope's filterable rabbit fibroma, the filterable tumours of fowls, or fowl leukæmia. Depression is characterized by cell necrosis and is well exemplified by the action of yellow-fever or Rift-Valley-fever virus on the cells of the liver, or of poliomyelitis on the anterior horn cells of the cord. In certain cases the characteristic action of the virus may be manifested after a very short incubation period—mice inoculated with Rift-Valley-fever virus die in forty-eight hours with extensive liver necrosis—or viruses may lie dormant in the tissues for many weeks or months, as in the case of rabies, Borna disease or lymphogranuloma inguinale virus when inoculated intracerebrally into mice. In scrapie, a disease of sheep, the incubation period is from sixteen months to two years.

In certain diseases the necrotic lesions are comparatively slight, but the resistance of the body to bacterial infection is greatly reduced. Sometimes the invading bacterium is specific, for instance, the virus of hog cholera is always associated with *Bacillus suipestifer*, the virus of swine influenza with an influenza bacillus. At other times, as in human influenza, measles, or

dog or cat distemper, the way is paved for the invasion of a variety of organisms.

In the case of certain viruses pathogenic action is restricted to the cells of one particular organ : other viruses are pathogenic for a variety of tissues. Many viruses display a special predilection for the cells of the central nervous system, while others, such as the viruses of yellow fever, Rift Valley fever, or horse sickness may, by intracerebral inoculation, be made to acquire such a predilection, at the same time losing many of their normal characteristics.

Inclusion bodies.—Histological examination of the lesions caused by many filterable viruses reveals the presence, either in the cytoplasm or in the nucleus of the cells, of peculiar cytological structures. These were at one period regarded as being themselves of a parasitic or possibly protozoal nature. The cytoplasmic inclusions vary greatly in type and in many cases their true nature is as yet unknown. The Negri body in rabies, for instance, may represent a stage in the complicated life-history of a parasite, or more possibly a reaction of certain cell structures to the presence of the virus. Certain cytoplasmic inclusions are undoubtedly made up of the virus particles, as in psittacosis, ectromelia, trachoma, lymphogranuloma inguinale, and smallpox ; or the virus particles may be surrounded by a cellular reaction, as in the Bollinger bodies of fowl-pox. The intranuclear inclusions, on the other hand, are more uniform in type. They occupy the nucleoplasm, may frequently be seen in the fresh unfixed cell, and tend to stain more or less intensely with acid dyes, such as eosin. Chemically they are not composed of chromatin, do not contain iron, and on micro-incineration yield only a fine ash. Closely similar structures may be induced in nuclei by the action of a number of chemicals. There is at present no direct evidence that they enclose the virus particles. Among the virus diseases which give rise to acidophilic intranuclear inclusions are yellow fever, Rift Valley fever, herpes febrilis, herpes zoster, varicella, Pacheco's parrot disease, encephalitis of silver foxes, pseudo-rabies, Borna disease, Virus III infection of rabbits, encephalo-myelitis of horses and " B " virus (*see* p. 348).

Cultivation.—One of the most important distinctions between viruses and visible bacteria lies in the fact that up to the present no true virus has been cultivated in the absence of living cells. The organisms of bovine pleuro-pneumonia, agalactia, and other pleuro-pneumonia-like organisms, which, formerly classed as viruses, can be grown on artificial media, are now generally regarded as true bacteria. Two methods are employed for the cultivation of viruses. The first method entails the use of an emulsion of minced embryo tissue suspended in Tyrode's solution and serum. The second consists in inoculating the virus on to the chorio-allantoic membrane of the developing chick embryo. On this membrane growth may entail either cell multiplication or cell necrosis.

Among the viruses which have been successfully grown by one or both of these methods are vaccinia, fowl-pox, Virus III infection, foot-and-mouth disease, yellow fever, Rift Valley fever, louping ill, rabies, and pseudo-rabies.

Filtration.—Various types of filter are used in the study of viruses. The most important are those composed of diatomaceous earth (Berkefeld or Mandler filters), porcelain (Chamberland candles) and asbestos discs (Seitz filters). Passage through these filters depends, not only on the size of the virus particles, but on a number of physical factors such as the negative pressure employed, the rate of filtration, the nature and pH of the medium in which the virus is suspended, and the electric charges of the filter and virus particles.

Recently Elford has perfected the technique of making graduated collodion membranes. which have enabled measurements to be made of the approximate size of the virus particles. Results so far obtained give the following approximate dimensions :

Psittacosis . . .	220 $m\mu$ to 330 $m\mu$[1]	(Levinthal, 1935)
Lymphogranuloma .	125 $m\mu$,, 175 $m\mu$	(Miyagawa et al., 1935)
Vaccinia . . .	125 $m\mu$,, 150 $m\mu$	(Elford and Andrews, 1932)
Rabies (fixed virus) .	100 $m\mu$,, 150 $m\mu$	(Galloway and Elford, 1932)
Herpes simplex . .	100 $m\mu$,, 150 $m\mu$	(Elford, Perdrau and Smith, 1933)
Rift Valley fever . .	23 $m\mu$,, 35 $m\mu$	(Broom and Findlay, 1933)
St. Louis encephalitis .	22 $m\mu$,, 33 $m\mu$	(Bauer, Fite and Webster, 1934)
Yellow fever . . .	18 $m\mu$,, 27 $m\mu$	(Findlay and Broom, 1933)
Louping ill	15 $m\mu$,, 20 $m\mu$	(Elford and Galloway, 1934)
Foot-and-mouth disease .	8 $m\mu$,, 12 $m\mu$	(Galloway and Elford, 1931)

Physical properties.—The resistance of viruses to heat varies within very wide limits ; to cold, on the other hand, many are extremely resistant and, especially when dried, they may survive for many months. Many viruses, such as rabies, are extremely resistant to the action of glycerin, others, like yellow fever, survive only a few days. Physiological saline or even Tyrode's solution is toxic to many viruses, but if serum is mixed with the fluid in the proportion of 1 in 10, it becomes much less toxic. Many viruses are very sensitive to the pH of the medium in which they are suspended, more especially when the reaction becomes acid. All the viruses so far examined carry a negative electric charge at pH's in the neighbourhood of neutrality. Many can be readily adsorbed on to finely dispersed substances, such as kaolin or animal charcoal, and, with the aid of suitable solutions, may be eluted from these substances, being thus obtained in a condition of relative purity.

The majority of viruses are easily inactivated by the photo-dynamic action of dyes such as methylene blue, or proflavine in dilutions of 1 : 50,000 to 1 : 100,000, when exposed to a pointolite. Certain viruses, such as that of dog distemper, when thus inactivated retain to a certain degree their antigenic properties. Certain viruses, also, when killed by formalin, are still antigenic.

Immunity.—With but few exceptions recovery from a virus infection is associated with a prolonged and sometimes life-long immunity. The few exceptions to this rule include herpes febrilis, the common cold, if it be really due to a virus, and dengue. Virus diseases thus differ as a class from bacterial infections, the majority of which do not leave an immunity of long standing. In many instances the prolonged immunity in virus infections is associated with the continued presence of virus in the tissues, but in others there is no evidence that it remains in a living condition in that situation.

Immunity is manifested by inability to reinfect with the same strain of virus as caused the original infection. It is important, however, to remember that in the case of certain viruses, such as foot-and-mouth disease and probably dengue, a number of strains exist which are antigenically distinct and give no cross immunity. In the serum, immunity may be manifested

[1] For value of $m\mu$, *see* p. 1042.

by the presence of virucidal, complement-fixing and, in certain cases, agglutinating antibodies. In the case of lymphogranuloma inguinale virus, a heated extract of the infected glands is capable of producing an allergic reaction when injected into the skin of an immune person, provided the infected material still contains virus particles.

Epidemiology.—The methods of spread of virus diseases are as numerous as in the case of bacterial infections. In certain instances direct contact with an infected person, as in the case of warts and trachoma, or with infected fomites is necessary, as in the case of variola or varicella. Lymphogranuloma inguinale and venereal warts are spread by sexual contact. Droplet infection is responsible for the spread of measles, mumps, influenza, and probably anterior poliomyelitis, though in the case of the last infection it is claimed that certain epidemics have been disseminated by infected milk. Insects may play a passive rôle, as in the transmission of fowl-pox, or may inoculate the virus by biting, as in the case of yellow fever, dengue, equine encephalomyelitis, Japanese type-B encephalitis, and phlebotomus fever. Louping ill of sheep is transmitted by the tick *Ixodes ricinus*. Many plant viruses are transmitted by Aphides or thrips.

Epidemiological considerations are dependent to a great extent on the immunity produced by a previous attack. When the number of non-immunes reaches a certain concentration an epidemic may break out. Inapparent infections may at times serve to maintain an infection. Many laboratory workers, without experiencing actual infections, have in the course of their work become immune to diseases as diverse in character as poliomyelitis, louping ill, or Rift Valley fever.

Treatment.—In only two virus infections has any drug been found to have a specific action: in lymphogranuloma inguinale and trachoma compounds of the sulphanilamide group are of very considerable value. In other virus diseases treatment is necessarily symptomatic. When once a virus has gained entrance to the tissue-cells, even the specific immune serum is without effect, although, when administered within a short time after the inoculation of the virus, immune serum may decrease the severity of the attack or even entirely prevent it.

In many diseases immune bodies are formed in the tissues a short time after the beginning of the illness: the patient may, however, subsequently die from the lesions which have been produced in the internal organs. Treatment must, therefore, be directed to maintaining the functions of the various organs, and to eliminating or destroying metabolic toxins.

Prophylaxis.—Prevention consists in destroying the virus and rendering the possible victims immune. In the case of those virus diseases which are transmitted by insects, much may be done by destruction of the particular vector, though in view of the wide areas over which a disease such as yellow fever is endemic, total elimination of the insect vector is well nigh impossible.

In view of the definite immunity produced by most virus infections, however, the possibilities of prophylactic immunization are considerable. Immunity may be produced by use of the following:

(i) Immune serum,
(ii) Immune serum and living virus,
(iii) Virus attenuated by physical or chemical agents,
(iv) Virus modified biologically.

Immune, or hyper-immune serum, is now largely used in measles prophylaxis. A temporary immunity only is obtained. Mixtures of immune serum and living active virus have been used in rinderpest and dog distemper. Virus attenuated or killed by physical or chemical means is also used in dog distemper and louping ill, while in rabies, fowl-pox, yellow fever, and African horse sickness, a biologically modified virus is employed, either alone, after further chemical or physical attenuation, or in association with immune serum.

It is probable that in the future prophylactic immunization will be extended to an increasing number of virus infections.

CHAPTER XVI

YELLOW FEVER

Synonyms.—Typhus icteroides; Fièvre jaune; Fiebre amarilla (Spanish); Gelbfieber.

Definition.—An acute, specific febrile disease, due to a filterable virus, occurring epidemically, or endemically within a peculiarly limited geographical area. Though subject to great variation and occurring sometimes in a very mild form, its typical clinical manifestations may be said to be characterized by an initial stage of sthenic nature, rapidly followed by an adynamic condition associated with bradycardia; toxic jaundice and albuminuria are liable to occur. One attack confers immunity for life. The virus is transmitted principally by the female domestic mosquito, *Aëdes ægypti*, formerly known as *Stegomyia fasciata* (*see* Plate IX and p. 995), which remains infective for life. Epidemiologically it is possible to distinguish three types, an *urban* form, transmitted by *A. ægypti*; a *rural* form transmitted by the same species; and, in South America, a *jungle* form transmitted by *A. leucocelænus*, *Hæmagogus capricorni* and certain Sabethine mosquitoes.

History.—The transmission of yellow fever through a mosquito was foreshadowed by Carlos Juan Finlay in 1891. A great advance in our knowledge of this disease was made in 1901 by the brilliant work of Reed, Carroll, and Agramonte, who showed that the causal agent could pass through filter candles; also by living among yellow-fever patients in mosquito-protected wards and surrounded by the excreta and vomit of these patients, they proved, by themselves remaining free from infection, that the transference of the disease under natural conditions takes place through the bite of the mosquito alone.

In 1928 Stokes, Bauer, and Hudson showed that the rhesus monkey (*Macaca mulatta*) is susceptible to the disease, and that the causal agent is an ultramicroscopic virus. The virus of the disease can be transmitted to rhesus monkeys through many passages by blood inoculation and can be conveyed by the bite of infected *Aedes* from one animal to another almost indefinitely. Recent researches have shown that in certain outbreaks and, under laboratory conditions, other mosquitoes are capable of transmitting the virus. The European hedgehog (*Erinaceus europæus*) and an African species (*Atelerix albiventris*) are also very susceptible to yellow fever.

In 1930 Max Theiler found that yellow fever may be transmitted to mice by intracerebral inoculation, producing in these animals meningo-encephalitis. After a number of passages in mice, the virus becomes fixed and on reinoculation into monkeys does not give rise to ordinary yellow

fever. The form of yellow-fever virus fixed for mice is now known as the "neurotropic" strain, in contradistinction to the ordinary or "pantropic" strain.

The discovery of the neurotropic strain of yellow-fever virus has been followed by the development of an efficient prophylactic inoculation.

"Jungle" yellow fever has been recognized since 1936.

Geographical distribution.—The International Health Division of the Rockefeller Foundation has greatly extended our knowledge of the geographical distribution of yellow fever. One attack of yellow fever produces immune bodies in the serum which last for life. By means of the mouse-protection test (*see* p. 359), it is possible to determine whether yellow fever has ever been present in a district, and, from the ages of those giving positive protection, when the last epidemic occurred.

In South America the disease is endemic in wide areas in Brazil, while recent epidemics have occurred in Bolivia and Colombia. There is also evidence that the disease exists or has existed recently in British and Dutch Guiana.

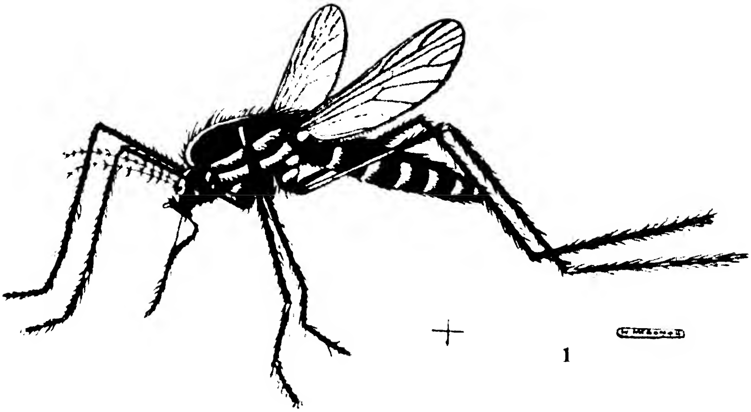
Up to 1925 it was the general belief that yellow fever had disappeared from South America, but from 1927–29 it was still found in Rio de Janiero. Next locally infected cases were observed in the Brazilian States of São Paulo, Minas Geraes, Rio, Bahia, Sergipe, Pernambuco, and Para. In 1930 the viscerotome was introduced for the purpose of obtaining liver tissue for pathological examination, and by its means the existence of jungle yellow fever was proved, in the absence of *Aëdes ægypti*, in Espirito Santo. Jungle yellow fever is now regarded as the original and more permanent form of yellow fever. It was found to be the cause of an outbreak at Santa Cruz de la Sevia, Bolivia, in the west of the continent.

A number of isolated cases have occurred among laboratory workers who have been engaged in the investigation of the disease; these infections, which number at least 35, have been due both to the pantropic and neurotropic strains of yellow-fever virus (Berry and Kitchen). Since the introduction of an efficient method of immunization these laboratory infections have ceased.

With more rapid means of transport there is danger that yellow fever may be introduced either by motor car or by aeroplane into new areas in Africa or even into India or China, for Eastern races of *A. ægypti* are as susceptible to infection as is the African. Adequate steps have been taken in aerodromes in all the endemic areas.

The history of the colonization and development of West Africa, especially Sierra Leone and the Gold Coast, is a story of a hard-fought struggle against yellow fever. In 1826, out of a garrison of 535 soldiers, 115 died within two months, and of the first detachment of troops to occupy Cape Coast Castle in 1823, only one was alive in the following year. In 1878 an epidemic occurred which involved the whole of Senegal; as many as 1,474 Europeans were stricken and out of 26 doctors, 22 died.

The last extensive epidemic of yellow fever on the Gold Coast occurred



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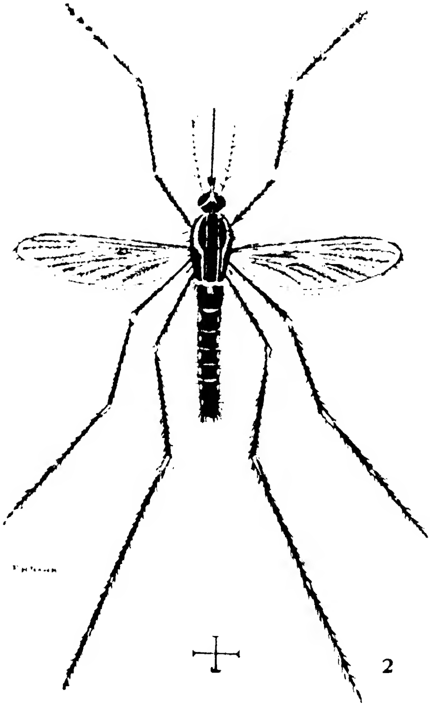

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Fig. 1. Aëdes (Stegomyia) variegatus. The buckled-up proboscis sheath is shown as in act of biting.

Fig. 2. Aëdes (Stegomyia) aegypti.

(The relative sizes are indicated by crosses.)

PLATE IX

in Accra in 1937. The feature of the epidemic was that it affected the native population more than the European. There was a small outbreak on the Congo at Matadi and Boma in December, 1927, and January, 1928, and in 1935 an epidemic occurred at Bathurst on the Gambia; there were numerous cases in West Africa in 1937 and 1938.

In Africa it has been shown, as the result of immunity surveys, that yellow fever is widely distributed in a region extending from the coast of Senegal eastward, for approximately 3,300 miles, to the upper reaches of the White Nile in the Anglo-Egyptian Sudan (Map IV). The northern boundary is the Sahara, and on the west it follows the Atlantic from Senegal to the extreme north of Angola. The eastern boundary is indefinite; positive sera are found in the western half of Uganda and in the Anglo-Egyptian Sudan as far east as the Abyssinian border. The southern boundary extends across Angola to the most southern part of the Belgian Congo. There is evidence of recent infection in the Nuba Mountains. This area has a maximal width of some 1,400 miles, and lies between the latitudes of 16° N. and 6° S. The reason why yellow fever has not spread to Kenya and Uganda is at present not understood.

Epidemiology.—Until comparatively recently, it was thought that yellow fever was confined to seaport towns and seldom spread far inland. A hundred years ago, it often occurred in epidemic form on board sailing ships at sea, and even spread from one ship to another while lying in port off the coasts of Portugal, France or Spain.

The histories of epidemics show that the virus of yellow fever can be transported from one place to another, and that for its development in epidemic form it usually requires a mean atmospheric temperature of over 75° F. (24–25° C.), but it is now recognized that the endemic centres have never extended beyond 40° N. Lat. and 35° S., where the isotherm is not below 20° C. It ceases to spread when the thermometer sinks below this point, and it stops abruptly as an epidemic when the freezing-point is reached. Dampness favours yellow fever; it is therefore most liable to occur and to spread during the rainy season. It does exist, however, in arid areas, and may occur in mountainous regions up to 4,000 ft. It has been found far inland. Villages are seldom affected by large epidemics; nor does the disease readily spread if introduced into rural localities. In advancing inland it follows the lines of communication—railways, canals, navigable rivers.

The urban form cannot continue to exist or spread in the absence of *Aëdes ægypti* mosquitoes in sufficient numbers. It may be that in this simple fact lies the explanation of many historic instances of the disappearance of yellow fever in the absence of any anti-mosquito measures.

Jungle yellow fever occurs solely in South America. It is present in orchard bush in Bolivia, Colombia and Brazil and is conveyed by the bites of *Aëdes leucocelænus*, *Hæmagogus capricorni* and certain Sabethine mosquitoes (*Sabethoides, Limatus, Wyeomyia, Goeldia,* and *Trichoprosopon*).

Immunity acquired by a previous attack.—It is now recognized that prolonged residence in an endemic area does not, in the case of Europeans, lead to immunity in the absence of an attack of yellow fever, while natives who pass through an epidemic unscathed do so because they have acquired an immunity as the result of a previous infection ; and thus arises the native adage, " White man, big fever : black man, little fever." It is of interest, however, to note that investigation of an area by the mouse-protection test, immediately after the subsidence of an epidemic, shows that the number of persons who give positive protection is very much greater than the actual number of cases clinically diagnosed as yellow fever.

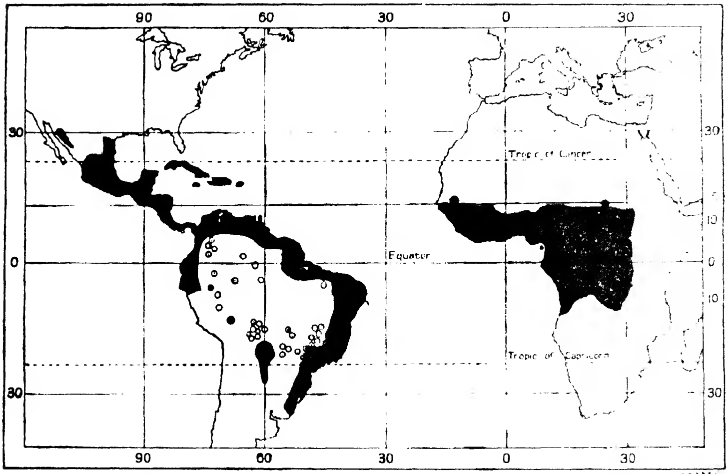
Rhesus monkeys artificially infected with an active pantropic strain of yellow fever usually die in from four to seven days after inoculation, before they have had time to develop immune bodies. Their tissues are therefore infective at the time of death. Human beings form immune bodies more rapidly and rarely die before the fifth or sixth day of fever, by which time sufficient have been formed to neutralize the virus ; it is present in an active state in the blood during the first three days of the fever.

The virus can pass, not only through the unbroken skin, but through the conjunctiva, while the neurotropic virus can infect through the nasal mucosa, and in these findings probably lies the explanation of the infection of laboratory workers who contracted the disease from a human case in England, and also of the laboratory infections which have sometimes proved fatal after post-mortem examination of monkeys.

In monkeys the virus can readily pass through the mucosa of the alimentary tract.

Incubation period of an epidemic.—Precise experiments indicate that the incubation period of yellow fever rarely exceeds four or five, with a limit of thirteen, days ; it may, it is said, be much shorter. In experimental infection of humans the shortest incubation period reported is two days. Occasionally it happened that the disease broke out in a ship after she had been several weeks at sea, having had no communication with the land or with another ship in the meantime. This was due to the introduction of infected mosquitoes into the ship before leaving port.

A period of at least a fortnight elapses between the arrival of a yellow-fever patient in a hitherto uninfected district and the occurrence of the first case of the epidemic he may give rise to. That is to say, that although, as stated above, the incubation period of yellow fever—the period elapsing between the introduction of the virus into the body and the oncoming of fever—is usually only from three to five days, yet a period of at least twelve days must elapse before that virus, after removal from one human body, can be effectively implanted in another. This is known as the extrinsic incubation period. Experiments with mosquitoes fed on monkeys show that the extrinsic incubation period may be reduced to eight or nine days if the mosquitoes are kept at high temperatures, but if maintained at low ones they may never become infected.



Black—Endemic at present day (1939). Shaded—Extent of virus of yellow fever as shown by the protection test. Circles—Distribution of "jungle yellow fever" in S. America, as shown by the Rockefeller Commission.

GEOGRAPHICAL DISTRIBUTION OF YELLOW FEVER

MAP IV

Conditions favouring endemicity.—In order that yellow fever may continue to exist in an urban community, three factors are necessary—(1) the virus; (2) the vector; (3) susceptible human beings living under conditions in which both parasite and man are easily accessible to the mosquito. A short break in this chain is sufficient to eliminate the disease. In the urban type, yellow fever cannot continue permanently in a community, unless the mosquito is present in sufficient numbers. In a population which is to a great extent immune from yellow fever it is obvious that a greater number of infected mosquitoes are necessary to maintain the infection. Instances are on record of the disappearance of the disease from towns in South America in which no sanitary work had been done to eliminate the mosquito. The possible explanation would appear to be the lack of enough susceptible persons to continue the life of the virus in man. Unquestionably, in its endemic areas yellow fever exists in a modified or "larval" form among the native children of the community, and the disease may only be recognized as such when it attacks non-immune immigrants.

Findlay has shown that the serum of about 25 per cent. of the monkeys in Central Africa is protective against yellow fever, and about the same proportion holds for those of the New World. In rural areas, therefore, yellow fever may persist in the absence of susceptible human beings. It is also a curious fact that normal cow's serum in certain instances protects.

In Ecuador the natives of the endemic zone round Guayaquil possess an immunity due to mild attacks of yellow fever in childhood, but natives of Quito, 300 miles distant, where there is no yellow fever, do not possess it, and many residents have contracted the infection on passing through Guayaquil to Europe.

Sawyer, Bauer and Whitman have shown, by means of immunity tests, that of 876 human sera from Asia and Australia, only two showed any protection against yellow fever, and among 481 sera from Italy, Portugal, Canada, and the northern U.S.A., and from some localities where the disease was formerly present, only one was protective. The nature of these odd cases showing non-specific virucidal substances in the blood is obscure.

Sera were also tested from the West Indies, Barbados, Cuba, Jamaica, Porto Rico, St. Lucia and Trinidad; 821 sera from persons under twenty years of age were all negative; but of the remaining 356, 30, or 8·42 per cent., gave positive protection tests.

In a total of 1,089 sera from Mexico:

5–9	years,	0·9	per cent. were positive.
10–14	years,	8·55	,, ,, ,, ,,
15–19	years,	28·81	,, ,, ,, ,,
20	or over,	42·72	,, ,, ,, ,,

From the Sudan, where yellow fever has not until recently been recognized, the examination of 43 sera from cases of jaundice resulted in the recognition of nine positives, eight of which came from the

Southern Sudan, and one from Wad Medani. Many villages in the Nuba Mountains show from 70 to 80 per cent. of positives, while those in the Fung area to the east of the White Nile are also infected.

Ætiology.—A great many attempts have been made in the past to discover the germ or virus of yellow fever, and a corresponding number of organisms have been described.

Reed, Carroll and Agramonte in 1901 showed that the causal agent was filterable. This was the first occasion on which a filterable agent was shown to be the cause of a human disease.

Stokes, Bauer, and Hudson clearly proved that the agent of yellow fever is ultramicroscopic and passes through Berkefeld filters V and W.

Sellards and Hindle have shown that the yellow-fever virus can maintain its vitality when frozen. Liver and blood from an infected monkey were collected in sterile tubes, frozen in a mixture of ice and salt for a period of twelve days and transported from Dakar to London, where, when inoculated subcutaneously or intraperitoneally into monkeys, the disease was reproduced. When frozen and dried the virus can retain its vitality for many years. A pantropic strain dried for seven and a half years killed a rhesus monkey in six days.

The observations which had been made upon the ætiology of the disease explained certain generally accepted facts: (1) The impunity with which a yellow-fever patient can be visited by a non-immune if outside the endemic area: the mosquitoes in the vicinity are not infective. (2) The danger of visiting the endemic area when the mosquitoes are both active and infective: *A. ægypti* usually feeds in the late afternoon, and the forest-living mosquitoes responsible for jungle yellow fever in South America bite during the day. (3) The discrepancy between the incubation period, three to five days, of the disease, and the incubation period, fourteen days and over, of an epidemic: the evolution of the germ in the mosquitoes infected by the original introducing patient demands the space of time indicated by the difference between these two periods. (4) The clinging of yellow-fever infection to ships, buildings, and localities: the persistence of the germ in infected mosquitoes (*Aëdes ægypti*), which are known to be capable of surviving for five months, and probably longer, after feeding on blood. (5) The high atmospheric temperature required for the epidemic extension of yellow fever: such temperature favours the activities and propagation of the mosquito and is necessary for the evolution of the germ in the insect.

A most important discovery has been that of Theiler (1930) in that *white* mice can be injected with yellow-fever virus by intracerebral inoculation. The disease produced is not yellow fever, but *meningo-encephalitis*, and after a certain number of passages in mouse brains, yellow fever of the usual type is not produced when monkeys are inoculated with the brain tissues of infected mice.

Although African monkeys are not immune to the viscerotropic strain of yellow-fever virus, they do not react by fever; the virus, however, circulates

in the blood for a time and immune bodies subsequently appear. South American monkeys are also susceptible. The clinical symptoms in rhesus monkeys are very similar to those of a rapid infection in man. Certain strains of pantropic virus are, however, much less virulent for monkeys than others.

The clinical severity of the human infection does not appear to bear any relation to the actual virulence of the virus, for Aragão (1928) produced fatal infections by inoculating monkeys with blood from benign cases of the disease. The " French " strain of virus, a very virulent one, was obtained from a Syrian in Dakar who showed febrile symptoms for a few days only.

Infection in rhesus monkeys with the pantropic strain can be produced by subcutaneous or intraperitoneal injection of infected blood tissues, by smearing yellow-fever blood on the unbroken skin, or by the mucous membrane of the alimentary tract. Infection may occur from the bite of even a single *Aëdes*.

The species of monkey which are susceptible to the pantropic strain of yellow-fever virus are: the Barbary ape (*Macaca inuus*), the rhesus monkey (*M. mulatta*), the crab-eating macacque (*M. irus*) the brown macacque (*M. speciosus*) and *M. sinicus*. In the latter species the infection is not fatal. Among New World monkeys marmosets usually die, while certain species of capuchin monkeys suffer from a febrile attack but do not succumb. Guinea-pigs are completely refractory, so that inoculation of this creature with suspected blood serves as a means of differentiation from *Leptospira ictero-hæmorrhagiæ*. The European hedgehog, *Erinaceus europæus*, regularly dies in from four to seven days after inoculation with pantropic virus, while *Atelerix albiventris*, Pruner's hedgehog from the Anglo-Egyptian Sudan, is also susceptible. Most laboratory animals, however, behave differently to intracerebral inoculation, as will be seen later.

There is a possibility that in certain rural areas a supply of infected mosquitoes may be maintained, in the absence of susceptible human beings, by feeding on monkeys or insectivora, which thus act as virus reservoirs.

Endemicity as ascertained by protection tests.—The fact that after an attack of yellow fever immune bodies are present in the serum for life, and that when mixtures of immune serum and virus are injected into susceptible animals infection does not occur, has given rise to the use of " protection tests " for the diagnosis of recovered cases of yellow fever. In the case of the pantropic virus a mixture of virus and the serum under examination is injected into a rhesus monkey; if the serum contains immune bodies the monkey does not die. This is known as the " *monkey-protection test*." When the neurotropic virus is used, a mixture of the serum and infected mouse brain is injected intraperitoneally into mice, which are at the same time inoculated intracerebrally with starch. If the serum fails to protect the mice develop encephalitis. This is known as the " *mouse-protection test* " (Sawyer and Lloyd). Both tests possess a very high degree of specificity and the results obtained by the two tests in the same areas of Africa and South America are in close agreement. The observations which have now been made indicate that, both in Africa and in South America, the areas which have been infected with yellow fever during

the lifetime of the present generation are very much more extensive than was previously imagined. Despite the non-recognition of outbreaks of yellow fever among native populations, it has been found that in Northern Nigeria, for instance, the populations of Ibadan and Ilorin yield 30·4 per cent. of protective sera; similar positive results have been obtained with sera from the French West African colonies and the Anglo-Egyptian Sudan. There is some evidence to show that infants who are being suckled by an immune mother are passively immune so long as they continue to feed on their mothers, while monkeys borne of immune mothers possess immune bodies at their birth.

Cultivation of the virus.—Haagen and Theiler succeeded in cultivating the neurotropic strain of yellow-fever virus in a medium of minced chick embryo suspended in a mixture of normal monkey serum and Tyrode solution. Even after one hundred passages there was no appreciable loss of neurotropic activity. No growth could be obtained in the absence of living cells. Lloyd successfully cultivated the pantropic strain which, after more than one hundred subcultures, has now become so attenuated that it can be used as a vaccine. Elmendorf and Smith have successfully grown the pantropic virus on the chorio-allantoic membrane of the developing chick embryo.

The neurotropic strain of yellow-fever virus.—When once the virus has become fixed for the brains of mice, it can be passaged indefinitely by intracerebral inoculation in these animals, though injected intraperitoneally it fails to kill; it is capable of producing a meningo-encephalitis not only in mice but in guinea-pigs, agoutis, squirrels, peccaries, capybaras, coatis, and field-voles, as well as in all species of monkey, Indian, African, and New World; viscerotropic lesions are not found. Rats, rabbits, hamsters, pigeons, hens and canaries do not suffer from an encephalitis. In hedgehogs, intracerebral inoculation may be followed by the occurrence of necrotic lesions in the liver. Inoculation of neurotropic virus intrahepatically in rhesus monkeys may cause reconversion to the pantropic strain. Spontaneous reconversion of a neurotropic virus with the production of pantropic lesions has occurred.

Physical properties of the virus.—The virus, both neurotropic and viscerotropic, passes readily through the ordinary filters, Berkefeld, Chamberland and Seitz. Findlay and Broom, by filtration through graded collodion membranes, have shown that the approximate size of the virus is between 18 and 27 $m\mu$. The virus of yellow fever is pantropic in the sense that it can produce lesions in all three embryonic layers.

Both the pantropic and neurotropic viruses are inactivated at a temperature of from 60° to 65° C. (Frobisher). When frozen and dried, the virus can retain its vitality for many months; it is also inactivated by the photodynamic action of dyes such as methylene blue (1 : 100,000) and proflavine (1 : 50,000) when exposed for short periods to a pointolite. The pantropic virus can withstand strong disinfectants such as mercuric chloride 1 : 7500, phenol 1 : 150 at 30° C. Both strains carry a negative electrical charge at the pH of the tissues.

Biochemical changes produced by the virus.—All the biochemical changes which occur in yellow fever can be interpreted as an interference with the liver there being no definite evidence of serious impairment of kidney function. Thus there is loss of glycogen from the liver and a considerable reduction in the blood-sugar. Findlay and Hindle have also shown that, as in other toxic affections of the liver, there is, in rhesus monkeys, an increase in the blood of guanidine-like substance. A similar increase is also present in human cases of yellow fever. The repeated administration of calcium lactate in large doses reduces this excess of guanidine and may play a part in preventing gastric hæmorrhage.

(1) *Transmission.*—The yellow-fever virus has distinctive characters and can be converted in the laboratory into a fixed neurotropic strain. Apart from the usual method of infection by the bites of infected mosquitoes, it is possible to acquire yellow fever through handling infected materials. Two hospital infections have been recorded in laboratory technicians in making blood slides and examining blood by biochemical methods. One of these proved fatal. There have been, moreover, severe and sometimes fatal infections resulting from post-mortem examinations of infected monkeys. It is recommended therefore that minute precautions should be taken in the post-mortem room; rubber gloves should be worn when taking specimens of suspected yellow-fever blood in an endemic area. Preferably all those likely to come in contact with yellow fever should have been immunized.

(2) *Transmission through the mosquito.*—The optimum temperature for development of the virus within the mosquito is 26° C., the extremes being 18–37° C., or in other words the atmospheric conditions of those localities in which yellow fever is endemic. Under natural conditions the percentage of mosquitoes which become infected is very small; possibly this may be explained by the small quantity of blood (0·01 c.c.) imbibed by *Aëdes ægypti.* There is no proof of hereditary transmission in the mosquito. The mosquito which is proved to be the principal vector for yellow fever is *Aëdes ægypti*, and many observations have been made upon its habits in so far as they affect the ætiology of the disease. It has been noted that the female mosquito does not lay eggs until she has fed upon blood, and that these are deposited about three days after feeding. It is generally stated—but this rule is by no means invariable—that before laying her eggs the mosquito is both diurnal and nocturnal in her feeding habits, but that subsequently she becomes strictly nocturnal, but this has recently been found to be incorrect. For further information on the habits of this mosquito, *see* p. 996.

The incubation period before a mosquito becomes infective has been shown to depend mainly upon the temperature. When the temperature is at 37° C. four days are necessary; at 21° C. eighteen days, but when kept at still lower temperatures (10–15° C.) the virus persists in mosquitoes without their bite becoming infective. The type of development appears to be simple, for if infective mosquitoes are ground up and fed in syrup to normal mosquitoes they, too, become infected after the usual incubation period.

The exact course of development of the virus in the mosquito has not been traced, but Aragão has shown that the virus is present in the alimentary canal for at least ten days after an infective meal, and

subsequently it becomes centred in the salivary glands. The virus undergoes multiplication in the mosquito.

Immunity.—The serum of patients who have recovered from yellow fever protects for life. Employing this protection method in monkeys and later in mice, the Rockefeller Commission in Nigeria have been able to detect the existence of yellow fever in villages where no signs of the disease had been noted.

Mosquitoes other than A. ægypti (formerly *Stegomyia fasciata*).—It has been proved in recent years that, under laboratory conditions at any rate, other species of mosquito are capable of transmitting yellow-fever virus. In South America certain epidemics have occurred in the complete absence of A. *ægypti* and certain jungle mosquitoes have been found infected, namely *Aëdes leucocelænus, Hæmagogus capricorni* and several Sabethinæ. Shannon, Whitman and Franca (1938) (*see* p. 355). The following mosquitoes also have been found able to transmit yellow fever by biting under laboratory conditions :

Culex fatigans.
European mosquitoes : *Aëdes geniculatus.*
African mosquitoes : *Aëdes vittatus, A. luteocephalus, A. africanus, A. simpsoni, A. stokesi, Mansonia africana, Culex thalassius, Eretmopodites chrysogaster.*
Asiatic mosquitoes : *Aëdes albopictus.*
South American mosquitoes : *Aëdes fluviatilis, A. scapularis.*
North American mosquitoes : *Aëdes triseria us.*

In a number of other mosquitoes the yellow fever virus remains active for considerable periods but is not transmitted by biting.

Pathology.—The olive-yellow colour of the skin is most marked in the dependent parts of the cadaver, especially in those parts which are subjected to pressure. Rigor mortis is pronounced. Petechiæ are common in the skin and serous membranes ; more considerable extravasations of blood may be found in the muscles. The brain and meninges are hyperæmic and may be studded with minute effusions ; like the other tissues of the body, they may be stained a lighter or deeper yellow. The cartilages are intensely yellow.

The blood in the vessels of the general circulation is not firmly coagulated. An important fact, as explaining the liability to passive hæmorrhages, is the existence of a generalized fatty degeneration of the capillaries and smaller blood-vessels. The stomach usually contains black or fluid blood. The folds of the gastric mucous membrane are swollen and there are aborescent patches of ecchymosis. The small intestine contains a dark material similar to that in the stomach.

The virus of yellow fever, like certain other viruses, has a particularly destructive action on the liver cells, and by a microscopic examination of liver sections alone it is usually possible to arrive at a diagnosis. If death has occurred at the later stages, the organ is usually somewhat friable and may present a yellowish colour which

has been compared with that of box-wood. The most marked changes are found in the mid-zonal region of the liver lobules, to a lesser extent at the periphery of the lobules. The liver cells are often separated one from another and tend to assume a rounded shape; a fatty degeneration may be very intense (Fig. 46.) Frequently the cytoplasm in whole or in part undergoes a hyaline degeneration—hyaline necrosis—together with hyaline bodies, first described by Councilman, while the cytoplasm of all the liver cells stains more intensely with acid stains such as eosin. The nuclei of the liver cells exhibit margination of the

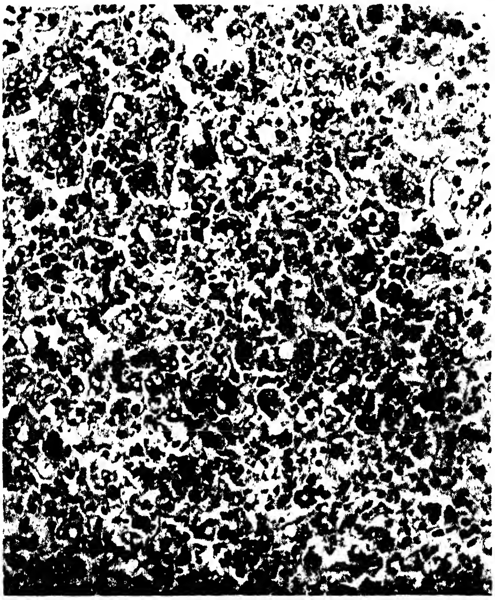


Fig. 46. Yellow fever: section of liver (low power) showing fatty and hyaline degeneration and Councilman lesions. (*Dr. G. M. Findlay.*)

chromatin round the nuclear membrane, while in some cells the nucleoplasm is occupied by acidophilic intranuclear masses (Fig. 47). Usually only a small number of cells are thus affected, but with certain strains 70–80 per cent. exhibit inclusions. In the rhesus monkey, a high percentage of cells always shows intranuclear inclusions. These intranuclear inclusions were first described by Torres and have been specially studied by Cowdry and Kitchen; they are similar in type to, though not identical with, the intranuclear inclusions found in many other virus diseases. Within the liver lobules there is found hyperplasia of the endothelial cells of the sinuses and an infiltration with large mononuclear cells and a few polymorphonuclear leucocytes. In the rhesus monkey the infiltrating cells are predominantly polymorphonuclear, while 80–90 per cent. of the parenchymatous cells contain acidophilic

intranuclear inclusions. Councilman lesions, on the other hand, are comparatively rare, while fatty degeneration is also less marked than in man.

In the spleen there are no characteristic changes, but the endothelial cells of the splenic sinuses may show hyperplasia, while the Malpighian corpuscles are somewhat atrophied. Definite changes, however, are found in the kidneys. Hæmorrhagic foci under the capsule and in the cortex are common. The renal epithelium shows cloudy swelling passing on to fatty degeneration which affects the tubules more than the glomeruli. The tubules, here and there, are filled with casts, either of an albuminoid material or of débris of

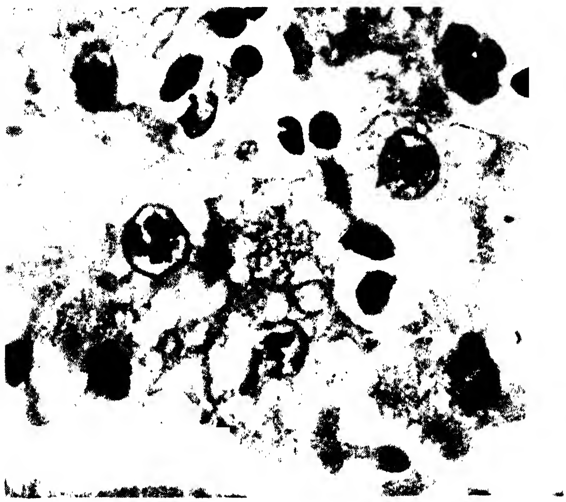


Fig. 47.—Yellow fever: section of liver × 2,000 showing acidophilic intranuclear inclusions and Councilman bodies. (*Dr. G. M. Findlay.*)

desquamated epithelium, corresponding with the casts in the albuminous urine. Hoffman regards the presence of lime-casts in the convuluted tubules as distinctive of yellow fever.

Symptoms.—There is the same variety in the initial symptoms of yellow fever as in other specific fevers. There may be sudden rigor occurring in the midst of apparent health; there may be only slight chills; or there may be a period of premonitory malaise leading up to the more pronounced symptoms; but high temperatures are not a feature of yellow fever. When fairly started, the procession of events is rapid. The incubation period is usually from three to six days.

Roughly speaking, and provided there are no complications, an attack of yellow fever is divisible into three stages—(1) the initial

fever; (2) the "period of calm," as it is called; and (3), in severe cases, the period of reaction.

The initial fever is usually sudden in onset, and lasts from three to four days. The maximum temperature is generally attained within the first twenty-four hours, or by the second day, and, in a case of medium severity, may rise to about 103° or 104° F. During the three or four succeeding days the mercury slowly sinks to 98° or 99°, the daily fluctuations being seldom more than a half to one degree. It occasionally happens that high temperature is maintained for more than three days, and also that the maximum is not attained till the

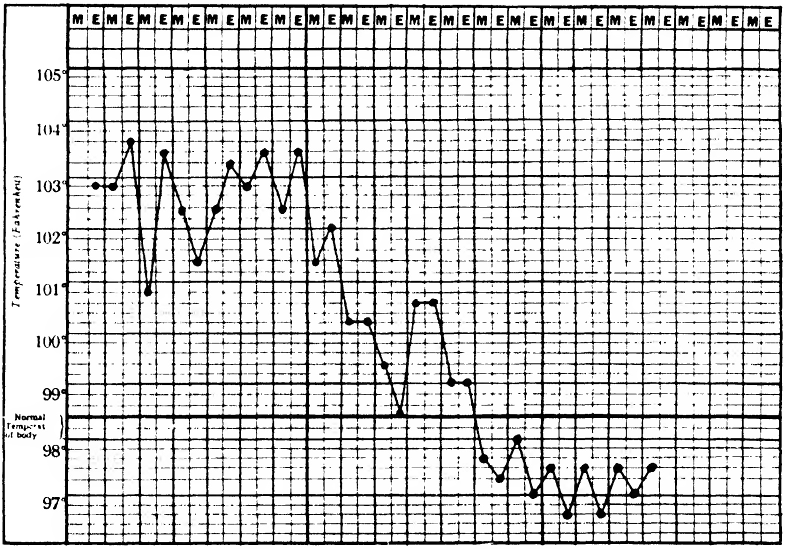


Chart 18.—Laboratory infection of yellow fever. Recovery.

eighth; as a rule, the thermometer behaves as described, the maximum being reached within two days of the onset of the disease (Chart 18).

With or soon after the initial chill or rigor, severe headache sets in and is generally a prominent feature. For the most part the pain is concentrated about the forehead, in the circumorbital region, and in the eyeballs themselves. In many cases it is associated with intolerance of light.

Loin pain is another very distressing symptom; it may amount to positive agony: the backache may be as bad as in a severe case of smallpox. The legs, too, ache excessively—particularly the calves, knees, and ankles; they feel as if broken. Epigastric pain is generally a prominent symptom.

The face is flushed and swollen; the eyes are shining, injected, and ferrety; the skin is dry.

What with pain and febrile distress the patient rapidly passes into a very miserable condition. He is restless and continually tossing about.

At first the pulse ranges from 100 to 120, and is full and strong; but as the disease progresses the pulse loses its sthenic character, gradually falling in force and frequency until, at the "period of calm," it becomes remarkably slow and compressible, beating perhaps only 30 or 40 times per minute. This fact may be of particular value in diagnosis, and is known as *Faget's sign*—that is, a falling pulse-rate with a constant temperature, or a constant pulse-rate with a rising temperature. It is in fact a sign which emphasizes the lack of correlation of temperature and pulse, so that by the second day, notwithstanding the high temperature, the pulse-rate becomes less, and by the third or fourth day it has probably decreased 20–40 beats from its initial rate.

At the outset the tongue is not very dirty, but it soon acquires a white coating on the dorsum, the edges remaining clean. It is not so swollen and flabby as in malarial fever; on the contrary, it is rather small and pointed throughout the disease. This is regarded as an important diagnostic mark; taken along with the progressive diminution in the strength and frequency of the pulse and the peculiar behaviour of the temperature, it is nearly conclusive as to the disease being yellow fever. Later, the tongue dries and, at the same time, thirst becomes intolerable. The palate is congested and swollen; the gums may also swell and bleed.

The congested appearance of the face at the onset of the disease tends to subside; so that by the time the asthenic stage is reached the features may have become small, the eyes sunken, and the eyelids discoloured by ecchymoses.

In some cases the skin is hot and dry throughout; in others it may be bedewed with perspiration from time to time; or the sweating may be constant, especially if collapse sets in.

By the third day the scleræ assume a yellowish tinge, and very often the skin acquires the yellow colour from which the disease derives its name. It must not be understood, however, that every case presents this colour of skin; in some it is entirely absent, but if carefully looked for there is always some yellowness of the scleræ to be discovered. The yellow tinging of the skin generally shows about the end of the first stage, deepening in intensity as the case advances, and remaining apparent for a considerable time after convalescence has become established. It ranges in depth from a light saffron tint to a deep mahogany brown. In fatal cases it is always present—not necessarily during life, but invariably after death. The skin in bad cases is said to emit a peculiar odour like gun-washings, or, as Jackson puts it, like the smell of a fish-market.

Petechial, erythematous, papular, and other eruptions may show themselves in different cases; but in yellow fever there is no characteristic eruption, unless it be an erythematous congestion of scrotum

or vulva, which occurs in a proportion of cases and is described as diagnostic. Bleeding from the gums is said to be characteristic.

An important feature, from the diagnostic as well as from the prognostic point of view, is the appearance, in some cases almost from the outset of the disease, of albumin in the urine, together with a tendency to suppression. This, according to Pichat, appears towards the end of the second day. In mild cases these features may be little marked; but in severe cases, particularly during the stage of depression, the urine may fall to a few ounces, and be loaded with albumin to the extent of one-half or even two-thirds (usually about 2 grm. of albumin per litre). The more pronounced these symptoms, the graver is the prognosis. It has been noted that the amount of albumin increases as the temperature falls. Urea (even during the incubation period) and uric acid are very much diminished, the former in severe cases falling to 1·5 grm. to the litre. The urine is almost invariably acid, depositing granular casts, and giving spectroscopic evidence of hæmoglobin. Bile-pigments and bile-stained tube-casts show themselves towards the end of the disease, usually about the fifth day, and their appearance is regarded as a favourable omen. Hæmorrhage from kidneys or urinary tract is not uncommon. The blood urea is usually high during the terminal stages.

Insomnia is usual, but if it occurs before the third day the prognosis is said to be grave. Delirium may occur, but is not an invariable feature. Usually, after the initial stage of restlessness and acute suffering, the patient becomes torpid, and perhaps taciturn. In bad cases coma, subsultus, etc., may gradually supervene, the temperature rising as death approaches, and even after. A well-marked *tache* is present on the forehead as well as on other parts of the body.

At the outset the bowels are confined. In the second stage, diarrhœa, perhaps of black material resembling the vomit (*see* below), may supervene; or there may be actual hæmorrhage of bright-red blood from the bowel.

Nausea and vomiting are more common than in other fevers. The well-known *black vomit*—always a grave symptom, but fortunately not by any means an invariable one—forms one of the most striking features of this disease. In the earlier stages of the fever, vomiting of bilious matters is a common occurrence. This may subside or, after a time, give place to a coffee-grounds vomit which seems to gush up without straining or effort on the patient's part, and which gradually deepens in colour until it becomes uniformly black. On microscopical examination the vomited material is found to consist of broken-down blood-corpuscles and altered hæmoglobin suspended in a yellowish mucoid fluid. This material is, doubtless, in the main derived from blood transuded through the walls of the capillaries of the mucous membrane of the stomach. It is intensely acid. Though the black vomit may not always be seen in fatal cases during life, the material is invariably found in the stomach post mortem.

Sometimes pure blood is thrown up from the stomach; similar passive hæmorrhages may take place from almost any part of the body—from eyes, ears, nose, mouth, bladder, uterus and so on. "Everything is congested at the outset, everything bleeds at the end," is a well-known adage in regard to this disease.

Death may occur during the early acute stage, being preceded by a rapid rise of temperature. The majority of deaths occur on the fifth and sixth days; the end seldom comes before the third or after the eleventh day, and, at this stage, it is generally preceded by a rapid fall of temperature.

In mild cases the "period of calm," which sets in after the subsidence of the initial fever, may last for several days before convalescence is established. The most constant symptoms are headache, pain in the back and extremities, photophobia, anorexia, prostration, congestion of the eyes, with a typical tongue, pointed and coated, but with red edges and tip. In such cases recovery, once begun, is usually rapid; in a week from the beginning of the disease the patient may be about again. In severe cases, however, the period of calm is followed by a third stage, the stage of reaction, in which the temperature again rises, though not to so high a point as in the initial fever, and a sort of remitting fever of an adynamic type keeps on for several days or weeks. This secondary fever is more prolonged if there is any complication, such as abscess, boils, parotitis, buboes, or hepatitis. The icterus is now very pronounced; black vomit may recur, or appear for the first time; perhaps a profuse diarrhœa ends in collapse; or the urine may be suppressed, stupor, coma, and other nervous symptoms ensuing, and very often ending in death. In other instances the secondary fever terminates in a crisis of sweating and a prolonged convalescence.

Even in Europeans, as illustrated by certain of the infections contracted in the laboratory, yellow fever may be comparatively mild and may resemble an attack of influenza.

Relapses are rare, and when they do occur are dangerous. The immunity produced by one attack of yellow fever is usually permanent, as permanent as that produced by smallpox or measles.

As a rule, there is no anæmia, but there is a slight leucocytosis early in the disease, soon followed by a leucopenia, which reaches its lowest point about the fifth or sixth day (Berry and Kitchen); the polymorphonuclear cells predominate, and there is an increase of mononuclear cells during convalescence. In human infections the virus has been shown to exist in the blood 107 hours after the onset of fever, while antibody has been detected after 83 hours, thus confirming what had already been suspected on epidemiological grounds of the simultaneous presence of virus and antibody in human blood in yellow fever.

Experimental yellow-fever infection in monkeys leads to a febrile reaction which is not high during the early days of the illness, but

subsequently there is a sudden rise of temperature followed by a rapid fall and the animal dies in coma. In some there is an alternating rise and fall and in others a rapid crisis and death. Death may take place as early as the fourth or as late as the fifteenth day.

Diagnosis.—Severe yellow fever may be confounded with *bilious remittent fever*, *infectious jaundice* (Weil's disease), *infective hepatitis*, and *blackwater fever*. The difficulties of diagnosis on clinical grounds are often great, especially early in an epidemic. When several deaths, preceded by fever and black vomit, have occurred within a limited area and in quick succession, a suspicion of yellow fever becomes a certainty. There is no clinical feature, so far as is known, which would distinguish a mild attack of yellow fever from an ordinary febricula, nor any pathognomonic clinical sign that would absolutely distinguish a malarial remittent from yellow fever and from infectious jaundice. *Dengue* is probably one of the most difficult diseases to differentiate from mild yellow fever. The facies, orbital pains, and backache are similar to those of dengue, but the appearance of the characteristic eruption of the latter disease on the fourth day should settle the diagnosis in any doubtful isolated case. Probabilities must be weighed in diagnosis when it is based on clinical grounds alone. The only reliable guides, as between malarial and yellow fever, are the discovery of the malaria parasite and the characteristic pigment and leucocytic variation in the one, and the determination of their absence in the other; and, when cases come to the post-mortem table, the presence of pigment in the viscera in the former, and of extensive fatty degeneration of the liver-cells in the latter. Occasionally the two diseases may coexist. The presence of albuminuria is of value in early and abortive cases. This is important in Europeans, though albuminuria is of very common occurrence in West African natives from any cause. Usually peptones appear with the albumin in variable quantities according to the gravity of the illness.

In addition to the diseases mentioned, there is great difficulty clinically in diagnosing yellow fever from Rift Valley fever, or, in its milder manifestations, from some forms of influenza.

It must also be remembered that in adults common infective hepatitis may also occur in severe form, while in addition unexplained outbreaks of fever and jaundice, not due to the yellow-fever virus, have been described from Nigeria—"Kukuruku disease" (Beeuwkes, Walcott, and Kumm)—and from Colombia, South America (Bauer and Kerr). "Dioundé", described by Stefanopoulo as occurring in French West Africa, also bears many resemblances to yellow fever. These diseases have only been differentiated by failure to infect rhesus monkeys during the acute stage, and by the absence of immune bodies to yellow fever in the blood. In Uganda and the Belgian Congo a virus which produces encephalitis in mice has been isolated from patients suffering from fever and jaundice. This virus is not neutralized by yellow fever immune serum. In West African natives particularly

jaundice and albuminuria are common accompaniments of lobar pneumonia.

Laboratory diagnosis.—With modern advances in our knowledge of the ætiology of yellow fever, an increasing confidence is being engendered in its diagnosis. Within the first three days of illness yellow fever is readily transmitted by inoculation of the blood to rhesus monkeys which die after an interval of at least four to five days. Blood which has been kept at the temperature of the ice-chest may retain its infectivity for several days. Direct inoculation of infected blood into the brains of mice gives rise to an encephalitis in from seven to fifteen days. For the diagnosis of recovered cases there is the monkey- or, preferably, the mouse-protection test

In fatal cases yellow fever may be diagnosed post mortem from a histological examination of the liver, the essential features being the fatty degeneration, mid-zonal necrosis, infiltration with mononuclear cells, and the presence of Councilman lesions (hyaline bodies) and acidophilic intranuclear inclusions. It must, however, be remembered that there is no one feature in the liver which is specific for yellow fever. The employment by the International Health Division of the Rockefeller Foundation of an instrument known as a "viscerotome" enables portions of liver to be removed from a cadaver without undertaking a general post-mortem examination. An examination of the livers of all those who have died from acute disease has, in South America, enabled many unsuspected cases of yellow fever to be accurately diagnosed.

Complement fixation.—Attempts have been made to discover some simple test for yellow fever which would tend to obviate the necessity of the more elaborate protective tests in experimental animals. Davis, Frobisher and Hudson have made numerous experiments using, as an antigen, either plasma, serum or liver obtained from monkeys on the first or second day of fever. The concentration of complement-fixing bodies was found to reach its maximum in monkeys after thirty to forty days, and they remained in the circulation for a few months to more than one year. Only inconstant results were obtained with human serum.

Prognosis and mortality.—Prolonged initial rigors, algidity convulsions, suppression of urine, coma, hæmorrhages, are all unfavourable symptoms. The prognosis is good if the temperature during the initial fever does not exceed 103° to 105° F. It is better for women (although, if pregnant, abortion is almost invariable) and children than for men; better for old residents than for new-comers; worst of all for the intemperate. According to a table given by Sternberg of 269 carefully observed cases, there were no deaths in 44 in which the temperature did not rise over 103 ; in 22 cases in which the thermometer rose to over 106° there were no recoveries. The mean mortality in the whole 269 cases was 27·7 per cent. In some epidemics it has risen as high as 50 or even 80 per cent. of those attacked, but the foregoing may be taken as a fairly representative mortality in yellow fever among the unacclimatized—something between 25 and 30 per cent. Among the permanent inhabitants of the endemic districts the case-mortality is very much lower—7 to 10 per cent. During epidemics, abortive and ambulatory cases occur; in these, icterus and other characteristic symptoms are often absent.

Such cases may be hard to diagnose from febricula or mild malarial attacks. In them the mortality is nil. Some epidemics are particularly mild : in others the majority of the patients die. In the same epidemic the cases may vary in severity from time to time. In children the mortality is insignificant.

Treatment

Formerly a much more active treatment than that in vogue at the present day was the fashion for yellow fever. It is now recognized that, as with most specific fevers, the treatment is more a matter of nursing than of drugs. Once in bed, the patient should not be allowed to get up. As in the case of other virus diseases the injection of immune serum is valueless once the infection has begun ; given during the incubation period, however, it may prevent or at any rate decrease the severity of the disease. Since the virus is efficiently neutralized by the formation of immune serum by the fourth or fifth day after the onset of fever, it follows that death is caused by the destructive effect of metabolic toxins on the liver, heart and kidneys.

Experience has shown that a smart purgative at the very onset of the disease is beneficial. With many, castor oil is the favourite drug, but to be of service it has to be given in very large doses—2 oz. or more. Others use calomel, or calomel combined with quinine. Others, again, prefer a saline.

Hot mustard pediluvia, frequently repeated during the first twenty-four hours, the patient and bath being enveloped in a blanket, are much in favour. They are said to relieve the cerebral congestion and the intense headache. Very hot baths, with subsequent blanketing and sinapisms to the epigastrium, are said to have a similarly favourable influence on the congestion of the stomach, which, is, undoubtedly, another constant feature of the disease. For high fever, antipyretic drugs, cold baths, iced injections, cold sponging, and the like may be carefully employed. In view of the asthenic nature of the disease, the less depressing measures should be preferred.

Vomiting may be treated with sinapisms and ice pills, or with small doses of cocaine. Morphia is dangerous and must be avoided. For black vomit, frequently repeated doses of perchloride of iron, ergotine injections, acetate of lead, and other styptics have been recommended. Calcium lactate in large and repeated doses by mouth is probably of value in counteracting the excess of guanidine present in the blood. The administration of glucose in the treatment of the hepatic conditions represents a distinct advance, and Le Fanu reports good results from this line of therapy originally suggested by Balfour. The glucose should be given in drachm doses by the mouth whenever feasible, or, when nausea is present, in 5-per-cent. solution intravenously (10 oz.), while injections of 5 units of insulin improve its assimilation. For restlessness, phenacetin or antipyrin is used. When the skin is

dry, the urine scanty, and the loins ache excessively, Sternberg recommends pilocarpine.

After the fourth or fifth day the flagging circulation demands stimulants of some sort. Iced champagne, hock, or teaspoonful doses of brandy given every half-hour may tide the patient over the period of collapse. Great care, however, should be exercised in the use of these things; if they seem to increase the vomiting and the irritability of the stomach they must be stopped at once.

Free ingestion of water tends to obviate the failure of renal function, which is the usual form of death.

The feeding is an important matter. So long as there is fever the patient has no appetite: during this time—that is, for the first two or three days—he is better without food. When the fever subsides appetite may return, and a craving for nourishment becomes more or less urgent: the greatest care, however, must be exercised about gratifying this untimely appetite. Only the blandest foods, and these only in very small quantities, should be allowed—such as spoonfuls of albumin water, barley water, iced milk or chicken tea. Gradually the quantities may be increased; but, even when convalescence is established, solid food must be partaken of very sparingly, and it must be of the simplest and most digestible description. Indiscretion in eating is a fruitful cause of relapse in yellow fever; and it must be borne in mind that in this disease relapse is exceedingly dangerous. Nutrition may be aided by nutrient enemata. Any slight exertion which may cause a rise in blood-pressure may be fatal. It is possible, too, that stimulation of the circulation incident to the taking of food may explain the dangers of altering food during the early stages.

The *Sternberg treatment* is directed principally to counteracting the hyperacidity of the gastric and intestinal contents—always a marked feature of yellow fever. The prescription is 150 gr. of sodium bicarbonate and $\frac{1}{3}$ gr. of mercury perchloride in a quart of water; of this $1\frac{1}{2}$ oz. is given every hour.

Any suspected case of yellow fever should be nursed under a mosquito-net day and night, and preferably in a mosquito-proof room.

Prophylaxis.—It is the duty of sanitary authorities in tropical countries to free from mosquitoes the areas over which they have charge, so far as possible. Although complete destruction is not to be expected, relative extermination of mosquitoes is worth attempting, and certainly much can be attained in this direction by the vigorous use of the now well-known measures. In Havana, by such means, in a very few months the number of mosquitoes was reduced 90 per cent., with a corresponding gain to the community in the diminution of mosquito-conveyed disease. The same happened in Panama, Rio and elsewhere. Rio de Janeiro has now been completely freed from mosquitoes.

All water-tanks, gutters, and cisterns must be effectually screened against *Aëdes ægypti* by fine-meshed metallic gauze; all puddles and stagnant water must be abolished and all holes in trees should be closed or the trees felled; all cases of any kind of fever, no matter how mild they may be, or what their nature, must be reported at once to the central sanitary authorities, who should have full powers promptly to screen or otherwise deal with them and the houses in which they originated. The general use of mosquito-nets must be insisted upon. Adult mosquitoes should be destroyed by swatting and the sprinkling of insecticides. The chief substance used in destroying adult aëdes in buildings is *Flit*, which is a mixture of pyrethrum, xylol, cresol, and methyl salicylate in paraffin. A mixture of carbon tetrachloride 7 per cent. with methyl salicylate 3 per cent. is also recommended.

Any delay in recognizing the earliest cases of a threatened epidemic is, as shown by experience in New Orleans, most dangerous, leading, as it may, to the rapid multiplication of infected centres.

Ships should not be allowed to clear from infected ports, nor to enter non-infected ports, during the warm season, without adequate inspection. The regulations of the International Aerial Convention should be enforced.

Aircraft.—In future it may be necessary, in view of the increasing facilities of air travel, to immunize all those proceeding from an endemic to a non-endemic area. It has been recommended by the International Sanitary Commission for Aerial Navigation that the measures for preventing its spread by aerial traffic should be taken primarily before departure from areas where the disease exists and only secondarily at ports of arrival. Measures to be taken before departure include the requirements that crews and passengers shall be free from any risk of infection during six days before embarkation and that the aircraft and cargo shall be free from the possibility of conveying mosquitoes. Methods of fumigation of aircraft and extermination of mosquitoes have been devised by Park Ross. There are several considerations which should modify the tendency to alarmist views of the danger of importing the yellow-fever virus to Eastern countries such as India or China, where the disease is so far unknown, but where climatic and hygienic conditions are favourable to its spread. One of these is the ease with which aerodromes can be kept free from yellow-fever mosquitoes, as well as the ease and rapidity with which aircraft can be cleansed of these insects.

In the United States it has been proved conclusively that *Aëdes ægypti* can be carried by aircraft for long distances, and the necessity of destroying these insects is insisted upon in all aeroplanes flying in tropical countries. Either fumigants or a spray may be used; among the former certain preparations of hydrocyanic acid give the best results, and the use of "discoids" (discs of unglazed paper soaked with liquid HCN) or Zyklon (fuller's earth impregnated) is recommended. They cannot, however, be used when passengers are already in the

'plane. As either fumigant or spray it can be employed easily and without danger by a skilful fumigator. Half an ounce of HCN per 1,000 cu. ft. may be regarded as the maximal dose for the killing of mosquitoes. The most efficient sprays are those containing a good extract of pyrethrin, except that pyrethrins produce a feeling of nausea in many persons. A concentrated extract is known as Pyrocide 40, but it is extremely dangerous and its use in Imperial Airways machines has now ceased. Owing to its high concentration of carbon tetrachloride it is liable to produce necrosis of the liver and cirrhosis, and has done so in rats and monkeys under experimental conditions. "Deskito," pyrethrins in glucose, is non-toxic and is now being employed ; it requires dilution before use. A 1 : 30 dilution of Deskito in water is employed, 150 c.c. for each 100 cu. ft. being necessary. The insecticide is allowed to act for fifteen minutes.

In addition to transport by aeroplane, there is danger that with increased motor traffic and better road communications infected persons will be able to travel from endemic to non-endemic areas in a time well within the incubation period of the disease. The regulation of all motor traffic from endemic to non-endemic areas has, therefore, to be carefully considered.

Should the disease appear in a locality which is not habitually a yellow-fever centre, and of which the population is small, an economical plan of dealing with the threatened danger is for the authorities promptly to remove the entire population of the neighbourhood, with the exception of the insusceptible and those in attendance on the sick, and to place the deported population, before dispersion, in a thirteen days' quarantine camp.

Prophylactic immunization may also be carried out on the whole population of an endemic zone of the disease, and would effectually check the spread of the epidemic. Recently the majority of the European population of the Gambia were thus immunized, and the method is now being extensively employed in West Africa and in South America, notably Brazil.

In the event of yellow fever breaking out in the crew of a man-of-war, the cases, if possible, should be sent ashore, and the ship hurried north or south into cold weather, any mosquitoes which may have found their way on board being at once destroyed.

In the case of the appearance of yellow fever in a large town, the method which was so successfully employed by the late Surgeon-General Gorgas must be adopted. Funds and authority must be obtained at once. An efficient and adequate sanitary staff must be promptly organized and instructed in their duties. Cases of every kind of fever, as well as cases of yellow fever, should be immediately reported, and the patients promptly protected from mosquito-bite by wire screens. At the same time the systematic destruction of mosquitoes in their breeding-places and in the patients' and neighbouring houses must be rigidly enforced. The infected houses should

be carefully sealed up by pasting paper over all the doors, windows, ventilators, chimneys, and cracks, and the fumes of pyrethrum or of burning sulphur—2 lb. per 1,000 cubic feet of space—or other insecticide employed to stupefy the insects, which should afterwards be swept up and burned. A viscerotomy service should be introduced.

Were it possible to immunize the whole population of the endemic areas in Africa and South America, and could this immunity be maintained for one year, the chain of infection would be broken and the disease finally eradicated.

Prophylactic inoculation was originated in America by Sawyer, Kitchen and Lloyd (1932), who employed the neurotropic variant of the French strain of yellow-fever virus. The patient was first given an injection of yellow-fever immune serum (0·5 c.c. per kilo. of body weight), and two hours later the virus in a filtered suspension in mouse brain was injected subcutaneously. Similar methods were employed in London, some 2,000 persons being immunized by this technique. In the French West African colonies, Laigret injected the neurotropic virus alone or mixed with egg-yolk or bile, immune serum being omitted. Severe immediate reactions were by no means uncommon, while a number of individuals developed nervous lesions characteristic of meningo-encephalo-myelitis.

At the present time in England and America the attenuated *pantropic* virus is employed for immunization purposes. The virus is grown in a medium containing inactivated normal human serum and Tyrode solution, in which a small quantity of minced chick-embryo tissue is suspended. After growth at 37° C., the virus is inoculated into eggs containing eight- to nine-day-old embryos for four days. The embryos are removed and ground up in normal inactivated human serum. At first the virus inoculum was combined with human immune yellow-fever serum, but for the past three years, owing to the attenuation of the virus, the immune serum has been dropped. In Brazil more than a million persons have been immunized, mass inoculation having been carried out under field conditions. In England more than 7,000 Government officials and others proceeding to West Africa have been immunized, and all Europeans going to countries where yellow fever is endemic.

Reaction following inoculation with the attenuated pantropic virus is either entirely lacking, or consists merely of slight headache and backache, lasting for about forty-eight hours. The only difficulty attendant on the inoculations has been the occurrence of 95 cases of jaundice in a series of 3,100 inoculations. The symptoms, which appeared in from 2 to 7½ months after inoculation, resembled in every way those caused by infective hepatitis. The explanation appeared to be that an extraneous hepatotoxic agent, almost certainly the virus of infective hepatitis (Findlay, MacCallum and Murgatroyd) had gained entrance to the tissue culture of yellow-fever virus. With a change in the strain of virus, this complication has now been entirely avoided.

After immunization with the pantropic virus, immune bodies begin to appear in the serum about the twelfth to fourteenth day, and are readily detectable by the twenty-first day. The duration of immunity to yellow fever following immunization is as yet unknown. In many persons immune bodies are detectable seven or more years after inoculation by the mouse-protection test. In a few, no serum immune bodies can be found six to twelve months after immunization. Reinoculation of such individuals is followed by a rapid rise in immune body titre, by a complete absence of reaction, and by failure to demonstrate circulating virus in the blood-stream. It is advisable that the blood of immunized persons should be tested every two to three years, and those who no longer show circulating immune bodies should be reinoculated. *Aëdes* mosquitoes are unable to take up virus from the blood after immunization, so that there is no reason why inoculations should not be carried out in areas where mosquitoes are present.

"Red Fever" of the Congo

Red Fever of the Congo, "Bakandjia," a disease which was thought to be yellow fever on account of similarity of the symptoms, has been shown by Findlay not to be yellow fever as thought by Clapier (1921), and also by Lefrou at Brazzaville in 1928 and called by him 'Fièvre rouge congolaise.' It more resembles dengue than yellow fever.

CHAPTER XVII

RIFT VALLEY FEVER

Synonym.—Enzöotic hepatitis.

Definition.—An epidemic disease of sheep and cattle in Kenya, caused by a filterable virus which is transmissible under certain circumstances to man. The best account of this disease is by G. M. Findlay, in 1932.

History.—Rift Valley fever was first described by Daubney, Hudson, and Garnham in Kenya in 1931; possibly the same disease was observed by Montgomery in 1913.

In 1912 a mortality-rate of 90 per cent. was recorded among the lambs born at the Government Farm, Naivasha (at an altitude of 5,500–6,000 feet), while other farms in the Rift Valley also suffered. In July, 1930, another similar outbreak occurred amongst the ewes and newly-born lambs, accounting for 3,600 of the latter, and 1,200 of the former in seven weeks. A high rate of abortion occurred. Focal necrosis of the liver was the chief pathological lesion at autopsy. During the course of the investigation, when the filterable virus was discovered, all four Europeans there employed developed a dengue-like fever with rigors and backache, whilst every native who had been engaged in herding these sheep had been ill for four days with fever and severe pains. A native volunteer was subsequently inoculated with the filtered virus and reacted with an acute attack of fever on the third day after inoculation; his blood was found to be infective to sheep for nine days afterwards. In addition to sheep and goats, cattle were found susceptible and a natural outbreak occurred in these animals at a farm sixty miles distant from the original outbreak.

The virus in blood, preserved in oxalate-carbol-glycerin, was brought to England by Daubney in 1932, was inoculated into lambs by Dalling and found to be as active as in Kenya, with the result that this investigator and his assistant, Hart, soon developed the same dengue-like train of symptoms. Subsequently other laboratory technicians have become infected.

Ætiology.—The virus occurs in the blood and appears to be present in the plasma and attached to the blood-cells; it is found in the blood, liver, spleen, and other internal organs, but not in the urine. The virus may pass through the placenta of pregnant animals and infect the fœtal tissues. The size of the virus particles has been estimated by Broom and Findlay to be between 23 and 35 $m\mu$. When present in plasma, or suspended in physiological saline at pH 7·2, the virus can pass through Berkefeld N.V. and W. candles, as well as through Chamberland L_2 and L_3 candles, without any loss in virulence. Blood preserved in oxalate-carbol-glycerin has retained its virulence for mice when preserved in the ice-chest at 4° C. for eight months. As in the case of yellow fever, the virus of Rift Valley fever is sensitive to

the hydrogen-ion concentration of the fluid; at pH 8·0 it is destroyed. Mackenzie (1933) has now succeeded in cultivating the virus without loss of titre in a medium of chick embryo and Tyrode's solution. The character of the virus remains unaltered. It can also be grown on the chorio-allantoic membrane of the developing chick embryo.

Mackenzie and Findlay, by repeated intracerebral passage in mice which had previously received intraperitoneal injections of immune serum, have succeeded in producing a neurotropic strain of the virus which causes an acute meningo-encephalo-myelitis in mice but little or no necrosis of the liver. Similarly, in monkeys and lambs, a fatal encephalo-myelitis follows intracerebral injection.

Apart from the susceptibility of sheep, lambs, and goats, the pathogenicity of the virus for man and monkeys (*Macaca*) and many small rodents (mice, field-mice, wood-mice, hamsters, dormice, and rats) is noticeable. Mice succumb in two to four days. Cats appear to be slightly susceptible. Indian and South American monkeys of the genera *Macaca*, *Hapale* and *Cebus*, are relatively susceptible, but African monkeys of the genera *Cercopithecus* and *Cercocebus* are relatively insusceptible, and do not suffer from any febrile reaction. Local East African rodents have been found by Daubney and Hudson to be highly susceptible to this virus, and probably play a part in its dissemination. These are *Arvicanthis abyssinicus*, *Mastomys coucha*, and *Rhabdomys pumilio*.

Using a mouse-protection test somewhat similar to that used in yellow fever, Findlay, Stefanopoulo and MacCallum have found that immune bodies can be detected in the blood of natives from the Nuba Mountains in southern Anglo-Egyptian Sudan, northern Uganda, and French Equatorial Africa; no immune bodies were found in bloods from West Africa.

Duration of infectivity.—In susceptible animals the infection can be transmitted by subcutaneous, intraperitoneal, intratesticular, or intracerebral inoculation, by application to the scarified skin, or by instillation into the nares or conjunctival sac.

In human cases which have been tested, the virus can be demonstrated in the blood for six days after the first rise of temperature, or nine days after the inoculation.

As in the case of yellow fever, it is probable that the apparent disappearance of virus from the blood and tissues is due, not to the death of the virus itself, but to its neutralization in the presence of immune bodies.

Pathology.—The pathological changes in animals consist of a focal necrosis of the liver. These foci may be discrete, as in sheep or goats, or may coalesce so as to involve the whole liver, as in young lambs, and in mice, rats, and other rodents. The histological changes consist of an infiltration with mononuclear and polymorphonuclear cells, and a hyaline degeneration of the cytoplasm of the liver cells (Councilman lesions). In the livers of infected mice, acidophilic intranuclear inclusions (or intranuclear bodies) have been found, by Findlay, as in many other filterable virus diseases, and similar bodies have been described by Daubney and Hudson in the livers of experimentally-infected sheep in Kenya. The nuclear changes in the affected cells are of the type known as "oxychromatic degeneration."

Symptoms.—In those cases which have been observed in man, the incubation period varied from four and a half to six days. At the commencement of the fever a feeling of nausea and a sensation of fullness in the hepatic region is experienced, and this is followed by violent headaches, pain in the

back, rigors, and general malaise. The face is flushed, and there is photophobia without, however, any marked conjunctival congestion. The tongue is thickly coated and epistaxis usually occurs. Bone pains are confined to the shoulders, back, and legs. The temperature varies between 101° and 102° F. On the fourth day of the fever the temperature falls to normal, accompanied by profuse sweating; a post-febrile weakness and a tendency to sweating on the least exertion remain. The bowels are usually constipated and the urine is deep yellow in colour. There appears to be an initial slight leucocytosis, followed on the third and fourth days by a definite leucopenia, which persists into convalescence.

One human case has been recorded in which the fever lasted for ten days, ranging from 101°–103° F., and showed a regular saddle-back character. The virus of Rift Valley fever thus produces in man a disease resembling in many respects dengue and phlebotomus fevers. In one instance three febrile attacks of decreasing severity were noted. One fatal infection in man has been recorded by Schwentker and Rivers (1934) from the Rockefeller Institute, New York. This occurred in one of the members of the staff who had been working with the virus. Although the course of the illness was otherwise typical, it was complicated by thrombo-phlebitis—a condition not previously described in association with this disease—and death was due to a pulmonary embolus. In the early stages the virus was present in the patient's blood and was pathogenic to mice. Death occurred on the forty-fifth day of the illness.

Immunity.—An immunity can be established in infected monkeys and it has been shown that they cannot be reinfected with massive doses of the virus for at least six months. In man immunity is present for at least seven years.

Diagnosis.—The virus of Rift Valley fever is distinguished from that of yellow fever by its pathogenicity on intraperitoneal injection for small rodents (mice and rats), and by the fact that monkeys (*Macaca*) immune to yellow fever are later susceptible to infection with the virus of Rift Valley fever. Human cases have also occurred in persons known to have suffered from yellow fever. The serum of recovered cases gives a specific complement-fixation reaction, and contains immune bodies which neutralize the virus when serum and virus are inoculated into mice. There is no relationship with dengue, phlebotomus fever, or psittacosis.

Treatment.—In human cases, treatment by injection of immune serum has been attempted by Findlay, though it is not possible to estimate the result. In view of the toxic action on the liver, glucose should be given by mouth.

Prophylaxis.—Evidently in the midst of a sheep epidemic human beings are themselves very susceptible to infection. There is some evidence to show that in the Naivasha district of Kenya, a mosquito—*Mansonia fuscopennata*—may be responsible for the transmission of the virus, whilst Daubney and Hudson now report that it is possible to convey the disease by inoculation of the body-contents of other mosquitoes, such as *M. versicolor* and *M. microannulata*. The neurotropic virus may be of value in immunizing sheep and cattle, since on subcutaneous injection it causes almost no reaction.

CHAPTER XVIII

PSITTACOSIS

Definition.—A disease of parrots, communicable to man, and occurring naturally in finches and other birds.

History.—The first definitely recognized epidemic of psittacosis occurred in Ulster in Switzerland in 1879, and there were seven cases with three deaths in the house of Dr. Ritter, where there were sickly parrots and some other birds. In 1882 there was a further small outbreak in Berne. In 1892 a large outbreak occurred in Paris, in which successive cases of pneumonia coincided with an importation of parrots from Buenos Aires. The homes of the two men who had imported the parrots became foci of human infection, one giving rise to 22 cases and 6 deaths, the other to 25 cases with 7 deaths. Dujardin Beaumetz reported that the human cases resembled influenzal broncho-pneumonia. Subsequently other fatal cases occurred in which the association with sick parrots was obvious, and Nocard isolated a bacillus allied to the paratyphoid group which was thought to be the ætiological agent of the disease. The Paris outbreaks smouldered on till 1897 when a somewhat limited one occurred in Italy, which was again traced to importation of Amazon parrots from Buenos Aires.

The first big outbreak of psittacosis occurred in Germany, in Cologne, in 1898, in which there was a distinct association with diseased parrots. The disease has also been met with in the United States since 1904. In 1917 an epidemic occurred in Pennsylvania in a store in which a number of sick parrots were kept. In England, prior to the epidemic of 1929–30, only six cases had been reported. It was in the course of this epidemic that the erroneous hypothesis of a Salmonella infection was abandoned and the true ætiology as a "filterable virus" established by Bedson, Western, and Levy Simpson. An epidemic among the personnel of the London Zoological Gardens in 1938, which resulted in five cases and one death, was due to the importation of parrots from the New World.

Epidemiology.—The recent outbreaks of psittacosis were at one time thought to have all arisen in Brazil, but no human cases have been reported in that country.

There is no evidence that epizöotics of this disease occur under natural conditions amongst the parrots in the forests of Brazil, but when these Amazon parrots, especially *Amazona æstiva*, are in captivity and are transported under grossly insanitary conditions to Europe, the disease arises and is able to spread.

A greater mortality from this disease occurs during the cold weather, as found by Gordon in budgerigars experimentally inoculated with psittacosis virus. The symptoms of psittacosis in birds are those of an acute infection. The infected bird sits listlessly, with ruffled and dirty plumage; it suffers from diarrhœa and there is usually a discharge from the eyes and nostrils,

Recently, however, this problem has been further complicated by the discovery of the virus in apparently healthy birds in California and in Australia, by Bedson, Meyer and others. When they are killed they are found to have enlarged spleens containing the virus.

The source of infection is usually the Amazon parrot, though grey African parrots have been the apparent cause in some of the British cases. In Australia a number of parrots caught in New South Wales have been found infected, while in the Northern Territory the Gouldian finch (*Polphila gouldiæ*) and the long-tail finch (*P. acuticauda*) carry the virus. The Bengalese finch, a cross between *Aidemosyne malabarica* and *Uroloncha striata*, imported from China, is also a carrier, as are the siskin and crossbill. Among the *Ploceidæ* the Java sparrow may show infection.

Possibly canaries, blackbirds and thrushes may occasionally act as carriers, and a disease resembling psittacosis has occurred in the Faroe Islands, where apparently it is propagated by the fulmar petrel, *Fulmarus glacialis* (Haagen and Mauer).

Parrots may remain in a subacute infectious condition for several years. Direct infection from man to man has been noted, and in one of the English outbreaks the doctor in attendance contracted this disease from his patient. House epidemics, too, are apparently not uncommon, particularly in Vienna, and, according to Gerlach, human beings may act as virus carriers after inapparent infections.

An infective pulmonary condition with a general typhoidal picture occurring in definite groups should suggest the probable diagnosis of psittacosis.

Ætiology.—The virus nature of psittacosis was worked out by Bedson and Western on the budgerigar (*Melopsittacus undulatus*), in which bird the disease is highly contagious. The virus can be transmitted by citrated blood or emulsions of liver or spleen. The blood contains the virus in the early stages of the disease and as long as the tenth day. Besides parrots and parakeets, hens are susceptible to the virus. Mice are susceptible to experimental infection by intraperitoneal inoculation and on intracerebral injection develop an encephalitis. These animals become acutely ill three or four days after injection and die of septicæmia with enlargement of the spleen.

The virus of psittacosis will pass Chamberland's L_1, L_2 and Seitz EK filters. The size of the virus is 23–35 $m\mu$. The amount inoculated into mice is 0·5 c.c. intraperitoneally. Rabbits and guinea-pigs are susceptible to intracerebral inoculation (Rivers and Berry), as is also the Tasmanian devil (*Sarcophilus ursinus*). The virulence of the virus is increased by passage through mice, and an intracerebral inoculation reveals a definite neurotropic tendency (Gordon). The virus of psittacosis inoculated intratracheally or intranasally in monkeys produces a pneumonia similar to that caused by the same active agent in man (Rivers and Berry).

In parrots which have succumbed to a fatal dose of the virus, minute bodies have been described in the endothelial leucocytes in and near focal lesions. These Gram-negative bacillary bodies have also been found in human tissues and have been described by Levinthal, Coles, and Lillie as *Rickettsia psittaci*. The forms described in the early stages of infections of the mouse with psittacosis are developmental stages of the virus, which, according to Bedson and Bland has a complicated life-cycle reminiscent of certain of the protozoa. These virus bodies can be readily demonstrated by Giemsa's and Castaneda's stains.

Pathology.—The pathology of psittacosis in the parrot has been

described by Lillie. A fibrinous or purulent pericarditis is produced with pericardial hæmorrhages. The liver is usually enlarged and studded with white foci of necrosis with red areolæ. On microscopic section this organ showed coagulation necrosis with oxyphil, pyknotic, karyolytic liver cells. Marked proliferation of the Küpffer cells was noted and focal infiltration by plasma cells and macrophages laden with fat.

Autopsy findings in man are those of a general septicæmia with inflammatory condition of the lungs. The spleen is normally enlarged and soft with semi-diffluent pulp. The most striking changes are found in the lungs, which exhibit a peculiar hæmorrhagic vesicular pneumonia, complicated by pulmonary thrombosis and a mucopurulent bronchitis in which bacteria are numerous. In the microscopic pathology one of the most striking features of psittacosis-pneumonia is the variation in type of the alveolar contents, often within the same microscopic field. Some alveoli contain serum alone; some serum and red corpuscles, and some leucocytes, macrophage cells and alveolar epithelium. An interstitial cellular infiltration has been noted in half the reported cases.

The lung changes were at first thought to resemble those of influenzal broncho-pneumonia, but they are now recognized as being of a distinct type. In psittacosis the consolidation is of a lobar type with abundant fibrin formation throughout the affected areas, there is practically no polymorph reaction, and hæmorrhages occur only in relation to the more severely damaged areas of the lung. The bronchioles are involved with the rest of the lung substance. In influenza the process is essentially a broncho-pneumonia and the lung is nodular in consistency. In the brain a condition known as "cerebral purpura" is not uncommon, masses of red cells escaping by diapedesis from the capillaries, the walls of which remain intact.

Symptoms.— Psittacosis in man is a severe illness with a high mortality (about 20 per cent.). All ages and both sexes are affected. The duration of the disease is two to three weeks. Convalescence is protracted and tedious and may be interrupted by temporary relapses or by femoral-vein thrombosis.

During the first week the patient may feel comparatively well, in spite of high pyrexia; the early symptoms are epistaxis and generalized pains. Towards the end of the week the whole aspect becomes more severe; the patient suffers from profound exhaustion and tends to become somnolent and intermittently irritable; there is usually a troublesome paroxysmal cough, which persists to the second week. Scattered signs of consolidation, which may eventually involve the greater part of the lung, become apparent. Constipation now becomes manifest and gives rise to tenesmus and abdominal discomfort. During the second week a state of semi-coma with muttering delirium sets in to such an extent that the patient's life is despaired of, but when things are at their worst, the temperature begins to fall by lysis, and in a few days the patient gradually shows signs of improvement.

Although the illness is usually severe, yet mild and even ambulatory cases have been recorded. The incubation period appears to be about eight to ten days but may extend to sixteen days. In man-to-man infections it is usually about four days. Pyrexia is usually of the typhoid type, and occurs in all cases; some cases have a gradual rise of temperature of the "step-ladder" variety.

Epistaxis occurs as an early symptom, usually on the first day. Sometimes it is noted as late as the eleventh to fourteenth day. Headache is a constant feature of the disease. Chills and rigors usually occur and with the latter a

temperature of 104° F. has been noted. Generalized influenza-like pains are the rule. The throat is usually sore and congested and in a few cases the tongue is swollen and sore in the condition known as "peribuccal œdema." The lungs are involved in almost every case, with a cough of varying intensity, but the sputum is scanty, and it may be rusty, characteristic of lobar pneumonia. The physical signs in the lungs vary considerably. A relative brachycardia is the characteristic feature of the cardiovascular system. Then with a temperature of 103° F. the pulse is about 90 and this feature adds to the typhoidal-like character of the disease—indeed the typhoid state is common in all the more severe cases. Photophobia is complained of and, towards the latter part of the first week most patients become definitely lethargic with stuporose appearance, sluggish speech, and blunted mentality.

"Rose spots" or similar skin lesions have been noted in nine British cases, and were observed at varying periods from about the seventh to the thirteenth days. The spots were on the chest and abdomen, more rarely on the back, measured 2–4 mm. in diameter, and definitely faded on pressure. Parotitis has been noted twice. The blood-picture in characteristic psittacosis of man is not markedly altered. Ambulatory cases frequently occur and may be the prelude to a fatal relapse.

Diagnosis.—On clinical grounds the diagnosis of psittacosis is not easy, as it has many features in common with typhoid. The gastro-intestinal symptoms may resemble those of that disease, but perforation and hæmorrhage never occur. The spleen is usually palpable in typhoid, but in only two out of 80 cases of psittacosis has it been palpable. With influenza, too, it has many features in common. Blood-cultures and agglutination reactions are completely negative in psittacosis and inoculations of blood or sputum in the early stages of the illness will prove fatal to mice. Apart from isolation of the virus, the only satisfactory method of diagnosis is by the complement fixation reaction. According to Bedson, the most satisfactory antigen is obtained from the spleens of infected mice, as it is essential to employ material that is rich in antigen. The technique is similar to that of the Wassermann reaction.

Differential diagnosis.—Psittacosis in parrots has to be differentiated from Pacheco's parrot disease, which was discovered by Pacheco, Bier, and Meyer while investigating pathological conditions of parrots in Brazil. The filterable virus produces a clinical picture similar to psittacosis; it differs from psittacosis virus in not being communicable to man or pathogenic to mice, while in the necrotic liver cells there are large acidophilic intranuclear inclusions.

Prognosis.—The mortality rate in human cases so far reported is high—usually about 20 per cent.—and convalescence is slow and tedious.

Treatment.—Symptomatic treatment and nursing should be on similar lines to those of typhoid. The only treatment which might be of any value is early use of serum of patients who have recovered from the disease. Injections of non-specific human serum appears to produce good results in some instances, while the sulphanilamide, prontosil, has been tried with good results in one case.

Prophylaxis.—The best method of avoiding a disease which is conveyed by birds of the parrot family is to avoid contact with these birds. Petting parrots, and especially permitting insertion of the beak into the mouth, should never be allowed. The importation of members of the parrot family and finches into countries where the disease is not endemic should be prohibited.

CHAPTER XIX

RABIES

Synonyms.—Hydrophobia; Rage (French); Tollwut (German); Lyssa; Rabbia (Italian).

Definition.—Rabies is an historical disorder among dogs and other animals. Under natural conditions it is transmitted both to animals and man by inoculation of virulent saliva in the act of biting.

It is now realized that it is caused by an ultra-microscopic virus which invades the central nervous system, by the peripheral nerves, and becomes fixed there. The incubation period is in some cases a very long one and the centres for respiration and deglutition in the brain are severely attacked, so that spasm and, eventually, paralysis result. Protection is afforded by inoculation with attenuated or killed rabies virus and to some extent by antirabic serum.

History.—The earliest recognizable reference to rabies is that of Aristotle in the fourth century B.C. The first extensive descriptions are those of Celsus in the first century A.D. and Cælius Aurelianus and Galen in the second. The paralytic form was first recognized by Van Swieten in 1771. The first actual demonstration of the identity of the disease in man and animals was made by Magendie and Breschet. The modern study of the disease dates from the classical studies of Pasteur, who devised the method of subdural inoculation of material from the central nervous system, and thus laid the foundations of the preventive system of antirabic inoculation which bears his name. He it was who also suggested that the causal agent might be an invisible microbe.

Geographical distribution.—There is no part of the earth where man and other terrestrial animals can live where rabies cannot potentially exist. Rabies occurs quite commonly in Greenland, Iceland, and other Arctic countries, but it is possible that in the Far North a special modified form of the disease exists. In the tropics and subtropics, especially where jackals and wild dogs abound, a specially virulent form is sometimes prevalent. In South America and in the West Indies, cattle are commonly affected[1] and constitute a reservoir of the virus, and it has recently been found in Jamaica that the "vampire bat" plays an important part in its dissemination. Australia is said to be free from this disease, and this freedom is ascribed to the peculiar fauna and the rigid quarantine which has been imposed upon dogs.

Rabies has been stamped out from Great Britain for nearly forty years, except for a small post-War outbreak among dogs due to an animal being smuggled into the country by aeroplane. It is very prevalent indeed in India, where, on account of the numerous and dangerous bites from wolves

[1] In South America rabies in cattle is—perhaps wrongly—termed "Mal de Caderas."

and jackals, it causes a high mortality. Statistics are difficult to obtain, but an average of about 5,000 persons are treated annually at the Pasteur Institute, Kasauli.

In the United States of America 10 states or territories only are considered to be free from the disease either in man or animals, and until recently it accounted for about 100 deaths a year.

Animals susceptible to rabies.—All warm-blooded animals are susceptible under favourable conditions to experimental inoculation of the rabies virus; it is more commonly met with in nature in those mammals which are subjected most often to the bites of dogs, wolves, and foxes. Some species are seldom infected because they are seldom subjected to bites, or because they are provided with thick fur.

There is some reason to believe that skunks, weasels, and stoats, and possibly the mongoose (*Cynictis penicillata*) may propagate the disease widely among their own kind, as does the dog. The susceptibility of rats to subcutaneous inoculation led to the opinion that these animals might also be capable of perpetuating this disease in nature, but of this there is now little evidence. In South Africa the meercats act as a reservoir, while in the United States grey squirrels have been found infected.

The domesticated animals are affected with the following percentage frequency: Dogs 85·1; cattle 10·7; horses 1·48; swine 1·12; cats 0·81; sheep 0·7; goats 0·09. Donkeys are rarely affected.

Wolves, foxes, and rabbits may be affected in different countries where they abound. Birds are relatively insusceptible to inoculation and this is said to be due to their high body temperature. Frogs are said to be susceptible.

The disproportionate prevalence of rabies during certain seasons of the year appears to have little foundation in fact.

Ætiology.—The symptoms of rabies indubitably point to an intoxication of the nervous system, while the pathological changes also indicate that this is the part of the body affected.

The most generally accepted view of the infection is that the virus of rabies, upon its introduction beneath the epidermis, finds its most favourable medium for propagation in the nerve-endings and fibres torn in the region of the bite. Along the course of the axis cylinders of these nerves it develops and travels, without disturbing their function, until the central nervous system is reached. The virus is strictly neurotropic, although Marinesco and Stroesco consider that the main path of dissemination is by the lymphatics. Finally the cells of the central nervous system are attacked, the first effect being excessive stimulation, leading finally to destruction. At the same time a neurotoxin is produced which is responsible for some of the symptoms. There is sound evidence that the explanation which has been thus outlined is fairly correct. Nerves leading from the site of the inoculation to the central nervous system have been shown to become progressively infectious in ascending segments, while complete section previous to inoculation confines the toxin to the lower segment. The blood and lymph appear to be incapable of taking up the toxin from the site of inoculation.

Street virus ("*virus des rues*," "*Strassenvirus*") is the strain found in the virulent nervous tissue infected by the natural disease[1]; its virulence is very variable and when inoculated subdurally into rabbits, it causes the symptoms

[1] The disease known as *Oulou-fato* among the natives in West Africa has been shown to be identical with rabies. Nicolau, Mathis, and Constantinesco claim that this virus is less virulent, and more difficult to fix, than is the true rabies virus.

of rabies to appear at a variable period of more than fourteen days. Inoculations should, if possible, be carried on for several passages, till the nature of the virus becomes clear. Considerable variation in street virus occurs, some strains showing rapid adaptation to the central nervous system.

Fixed virus (*virus fixe*) is modified from the street virus by passing it through a long series of rabbits. In this manner its virulence becomes greater for these animals, so that finally they develop the disease after a constant or "fixed" period of incubation, so that no amount of further *passages* can reduce the incubation period below the span. The mouse, however, appears to be the most suitable animal for rapid diagnosis.

Nicolau and Kopciowska have been able to pass a strain of rabies virus from sciatic nerve to sciatic nerve for more than one year, and have thereby re-converted "fixed virus" into "street virus." The strain of fixed virus had been passaged in the laboratory for six years and gave rise to from one to four Negri bodies in 100 ganglion cells of the horn of Ammon. The transformation was achieved by passage inoculations made into the right sciatic nerve, the emulsions employed being obtained from the *left* sciatic nerve of the previous animal. With a great amount of trouble two lines of *passage* have been obtained covering a period of more than a year.

Negri "bodies."—Negri originally described certain oxyphilic granules in the nerve-ganglia cells of the Ammon horn of the brain. Although probably they are of the same nature as the inclusion bodies found in association with other ultramicroscopic viruses, yet they were formerly regarded as parasitic in nature. Calkins classified them as sporozoa—*Neurocytes hydrophobiæ* (also called *Glugea lyssæ.*) Levaditi believes that the Negri body represents one stage in a complicated life-cycle. Negri bodies are admittedly very constant in rabies and peculiar to it. In the majority of cases they are used for diagnosis, but it must be admitted that their exact significance is still in dispute.

Covell and Danks, after microincineration and other studies, conclude that the Negri bodies arise from constituents in the nerve-cell as a result of the virus. It must be remembered that they are not present in every case of rabies, but when a person has been bitten by an animal having symptoms suspicious of rabies, preventive treatment should at once be instituted. Inoculation tests have shown that this practice is sound. The custom of killing suspected animals immediately after they have bitten their victim is not to be recommended, as it operates against the demonstration of Negri bodies which may be present in the later stages of the disease. Other changes in the nervous tissue, of less importance from a diagnostic view, have been described, and Courmont and Lesieur claim that in the dog there is present a relative polymorphonuclear-leucocyte increase in the blood and in the lungs; whereas in the normal dog this constitutes 53 per cent., in the rabid animal it forms 90 per cent.

Passage of virus in carnivorous animals—When passed through dogs the virus does not lose its potency; on the contrary, it becomes fixed with an incubation period of eight or nine days, but in rats *street virus* becomes rapidly augmented in virulence; on the other hand *attenuation* and a final *loss* of virulence is obtained when monkeys, frogs, and birds are inoculated.

Location of the virus in the body.—The central nervous system and the peripheral nerves contain the virus with constancy, but the infectiousness is variable in different parts of the nervous system. It was found by Nitsch that 0·1 mg. of the brain cortex (*fixed virus*) was lethal to rabbits in seven to

nine days, whilst 0·5 mg. from the middle of the cord was not virulent, but 1·0 mg. was. The medulla, for instance, is five times more virulent than the rest of the cord. The salivary glands of dogs are constantly infectious. The generally accepted idea is that the virus finds its way to the salivary glands by way of the nerves and, according to Remlinger, the saliva of a dog may remain virulent five days after apparent recovery from rabies. In man the salivary glands are seldom invaded. The blood is non-infectious either in man or in experimental animals. There is no evidence that the virus can be conveyed to the fœtus. Neither the milk, urine, liver and spleen, nor spermatic fluids ever harbour the virus.

Cultivation of the virus.—Although there is considerable doubt whether the virus can be successfully grown in the chorio-allantoic membrane of the developing chick embryo, it has been grown successfully either in a plasma medium or in Serum-Tyrode containing mouse- or chick-embryo tissue. Human and monkey were more satisfactory than rabbit serum.

Properties of the virus.—The particle size of the virus of fixed rabies is 100–150 $m\mu$, as determined by filtration. Centrifugation renders the supernatant fluid of an emulsion avirulent. The virus is sensitive to heat, since ordinary undried emulsions lose virulence after exposure to 50° C. for sixty minutes and 60° C. for thirty minutes. In the dried form, however, the virus resists 105° C. for two minutes. On the other hand it can resist intense cold (liquid air at —190° C.) for three months. It is resistant to 50 per cent. glycerin for many months.

Desiccation.—Rapid desiccation of brain and spinal cord is not destructive to virulence, and rapidly desiccated virus can be preserved in stoppered bottles in the dark for nine months. Gradual desiccation at higher temperatures (23° C.) is accompanied by gradual attenuation of the virus, so that virulence is usually lost in five or six days.

Filtration.—Emulsified rabies virus passes through the pores of Berkefeld filters, but not finer than L_3 in the series of Chamberland bougies, and it is claimed that fixed virus passes through even finer pores than street virus.

Chemical agents.—Rabies virus is sensitive to the action of acids and alkalis, but more resistant to chemical disinfectants than are bacterial emulsions. It is probable that when introduced into the subcutaneous tissues leucocytes and other cells are capable of *absorbing* the virus. The serum which is immunized against rabies is able to destroy the activity of the rabies virus *in vitro*. From immunized sheep a serum of a very high antitoxic titre has been obtained.

The Trinidad disease (Paralyssa).—Hurst and Pawan (1930) have described a curious paralytic form of rabies in the island of Trinidad. It appears especially to affect and be spread by the vampire bat, which in the whole of South America and in the Antilles feeds indiscriminately on the blood of man and cattle. The disease was first noticed in five cattle, and subsequently five cases were discovered in man. The virus was transmitted to monkeys, and further studies have been published by Hurst and Pawan. This disease of cattle is apparently identical with the " mal de caderas " of South American cattle, probably better termed South American *lyssa.* Some doubt has been expressed whether the bat at first identified by Pawan was the vampire (*Desmodus rufus*) or a harmless species, *Artibœus.* Now Lima (1934) in Brazil has, by direct experiment, brought forward evidence that in the State of Santa Catherina epizöotics are prevalent in the favourite haunts of vampire bats (Desmodidæ) and that the transmitter is the local species (*Desmodus*

rotundus). The virus may be demonstrated in the saliva of bats, which act as healthy carriers for considerable periods. Kraus and Duren have suggested the title of "*Paralyssa*" for this form of the disease.

Incubation period of rabies.—In rabies this is remarkable for its length and great variability. In nature it is seldom under ten days, but may extend to a year, or even longer, though the majority of cases occur before the end of the third month.

The length of the incubation period is influenced by the following factors —the species of animal: it is usually longer in man than in the lower animals. The site of the inoculation: the shorter the distance from the brain, the shorter will be the period of latency, whilst females exhibit a shorter period than males, and children than adults. The severity of the wound and the physical condition of the patient have undoubted influence.

Symptoms and clinical course.—Rabies presents two distinct clinical types. There are the furious or excited, and the quiet and "dumb" or paralytic. Some distinguish four types of the disease, cerebral, medullary, cerebellar, and sympathetic.

The excited or furious type.—The onset of rabies is usually rapid and the patient usually shows some psychical change very early, becoming anxious, melancholy, and possessed of strange presentiments. Sleep becomes impossible. Soon local numbness, twitching, and a sense of itching progress centrally from the wound, which becomes engorged and tender. Sometimes the first symptom complained of is a strange sensation in the throat, and a sense of constriction of the fauces.

The mental symptoms may be purely hysterical and there are many cases recorded in which the onset is determined by mental shock. Fright and terror may be regarded in many instances as the manifestation of the disease. An initial rise of temperature is perhaps the most constant early sign.

The prevailing symptoms may last several days before the decided outbreak, but usually only twenty-four to forty-eight hours. *Hydrophobia*, the outstanding symptom, prevails in the great majority of cases, and it arises from the extremely painful spasms of the organs of deglutition and respiration which are induced in attempts to eat and, especially, to drink.

These spasms are of such an agonizing character that they exceed, possibly, all other forms of human suffering, consequently the sight or smell, or even the sounds of liquids, is sufficient to bring on an attack. When an effort is made to gulp down a small quantity of liquid it is freely expelled, with an accompanying and anguishing spasm of the throat and larynx. The condition is a state of hyper-susceptibility of the nerve-cells to external stimuli. Draughts of air may bring on a convulsive seizure; skin and tendon reflexes are exaggerated, the respiratory spasms involve the thoracic muscles and cannot be relieved by intubation. Solid foods are usually more readily taken than are fluids.

Whenever the onset is determined the disease progresses rapidly. In the majority of instances there may be periods of latency which cause the hope of recovery, and doubts may be entertained as to the correct diagnosis. The mind is usually exceptionally clear, questions being answered with intelligence until the voice becomes indistinct and the words unintelligible. There are periods of excitement which may be truly maniacal; the patient may injure or destroy any objects near at hand, but there is seldom any tendency to injure other persons. Sexual excitement, accompanied by priapism, is a frequent symptom. The voice usually becomes hoarse; the

strange sounds emitted during expectoration at the onset of the seizure have given rise to the popular conception of "barking like a dog."

The convulsive seizures become more and more pronounced till a condition of paralysis leads to death. The muscles, which have been racked to the limit of endurance, become limp, and the face, which has expressed the acme of terror and suffering, becomes expressionless. There is usually an excessive secretion of ropy saliva which the patient is unable to expel. Finally, the breathing becomes irregular and feeble and at last stops altogether. The temperature rises before death. Sugar and acetone are usually found in the urine. In the paralytic stage the pupil is dilated.

The paralytic type in man.—Because its symptoms are less marked than in the violent type, it undoubtedly remains unrecognized in many cases. For a time the mere existence of this form was forgotten. Pathologically it has been attributed to infection with a large amount of virus and to the involvement of the spinal cord rather than the brain. The onset is with high fever, general malaise, headache, and vomiting; afterwards there is localized pain, especially in the bitten parts; a heaviness and numbness of these parts follow, then ataxia and weakness, and finally paralysis. Girdle sensation is usually complained of.

Consciousness is retained until late in the disease. The paralysis spreads with preceding or accompanying pains of the affected parts, involving limbs, trunk, rectum, bladder, face, tongue, and eye muscles. More or less difficulty in swallowing liquids results from the respiratory embarrassment, but the symptom of "hydrophobia" is usually absent. Frequently normal respiration may be restored for a time and death takes place from cardiac paralysis.

This form of the disease is more prolonged than the furious type, lasting up to seven and a half days, as compared to the average duration of three to four days in the former.

Rabies in the lower animals.—On account of its highly developed intelligence through centuries of intimate association with man, the dog shows the most marked psychical disturbances, and when a dog begins to exhibit marked and causeless changes in usual disposition, suspicions of rabies should be entertained, especially if there are other reasons for such suspicion. The dog may become more morose, sullen, or irritable, or show excessive affection, and fatal infections are liable to occur at this stage through licking wounds or abraded surfaces.

A very characteristic symptom is the change in the character of the voice, which is said to resemble the yelping of a tired foxhound giving tongue. The rabid dog is easily startled, growls and barks on the slightest provocation. When the dog seems mad he usually bites many other persons and other animals. He bites them, or passes by, but never swerves out of his way to attack them.

The popular idea of a rabid dog is an incorrect picture. On the other hand, it looks ill, takes no interest in its surroundings, trotting along with a wavering gait, and often with unilateral drooping of the ear. Convulsions soon appear and the animal may die during one. More frequently, a paralytic stage supervenes and the dog drags himself to a secluded spot. In place of its accustomed appetite, it swallows sticks and stones and other objects. Swallowing, at first difficult, later becomes impossible.

The *paralytic form* is most frequent amongst dogs and is peculiarly dangerous to man. The dog becomes the object of sympathy, and often bystanders become scratched or bitten. Such rabid dogs are intensely

thirsty and have no fear of water, but owing to the paralytic condition of the throat they are unable to swallow. Glycosuria is a common symptom of rabies in animals and is said not to be of renal origin.

The *paralytic* form is very common in herbivora, but horses present the most agonizing type of the furious form.

Experimental rabies in the rabbit.—After subdural inoculation, rabies manifests itself by a premonitory fever ; the animal appears sleepy and does not eat. The appearance of the face is characteristic ; the eyes have a staring expression and frequently there is drooping and lopping of one ear. The animal urinates more frequently than normal. Rarely a furious stage occurs, convulsive seizures are frequently observed and there is grinding of the teeth. Paralysis begins in the hind legs and proceeds forwards. Abortion is common in pregnant females.

Immunity.—Natural immunity to rabies is exhibited by a number of lower vertebrates ; occasionally in mammals an *individual immunity* may be observed, and a state of *hereditary immunity* has been described by Remlinger and Konradi.

Much more is known about acquired immunity. Man and animal may be rendered immune by inoculation with the modified virus of rabies ; secondly, their blood acquires " rabicidal " properties, that is, the power to render inert the virulent material exposed to its action *in vitro.*

The virus is more virulent in rabbits, inasmuch as it causes the disease more quickly, but at the same time it loses its virulence for animals higher in the taxonomical scale. It is assumed that by passage through rabbits the virus becomes increased, hence the early onset and the paralytic symptoms. Its resistance to the inimical action of the body juices is thought to be reduced, hence the harmlessness of subcutaneous injection. The arguments in favour of the toxin of rabies being in the nature of an ultramicroscopic virus are as follows : the production of symptoms of fever, emaciation, and cachexia by virus which has been passed through a filter. Glusman, Solonjowa and Predtetschenkaya have found that the virus can pass through Chamberland bougies L_2 and L_3. Occasionally during the inoculations, or soon after, paralytic symptoms appear, apparently not directly due to rabic infection, paralysis of the Landry type being noted. These paralytic accidents are occasioned, it is believed, by some toxic substance present in nervous tissues both from rabid and normal animals.

Immunity to rabies can be conferred by increasing doses of filtered emulsions and those exposed to high temperatures.

Levaditi and Stoel have shown that the virus of rabies is maintained, and probably multiplies, when placed *in vitro* in contact with cellular elements. The virus develops in contact with embryonic cerebral tissue *in vitro*.

There are other peculiarities of the rabies virus toxin, for the spinal cord of the rabbit, when dried until it has lost its infectious properties, has also entirely lost its immunizing properties. It is therefore possible to explain the artificial immunity conferred by the injection of *fixed virus* as follows : The successive injection of dilutions of fixed virus, increasing from weak to strong, or of emulsion of the dried cord has this effect : The rabies toxin contained within them arrives earlier at the cells of the central nervous system by way of the blood and lymph circulation than does the slowly progressive growth of the rabies virus along the nerves, so that when it arrives at the nerve centres, the protoplasm of the nerve-cells has already become accustomed to the action of the rabies toxin and consequently the

virus, introduced during preventive inoculation, can no longer affect the nerves and produce chromolytic changes in them. Unattenuated "*fixed*" *virus* may now be used for the production of immunity, for there is no danger of producing rabic infection from the *subcutaneous* injection of this substance. It has recently been shown that in the presence of a pointolite, rabies virus may be inactivated by the photodynamic action of dyes, such as methylene blue or proflavine in high dilutions. Inactivated virus, however, retains its antigenic power.

Diagnosis and differential diagnosis.—The diagnosis of rabies rests upon the consideration of many factors, such as the history of exposure to infection, the length of the period of incubation, the clinical symptoms and course, the termination, and the post-mortem findings, confirmed by inoculation tests on animals.

In recounting the history of exposure to the virus, due consideration must be given to the mental excitement of the patient and to the fact that the rabies may be infectious several days before the appearance of rabid symptoms in infected animals.

Very often it happens that no history of infection may be obtained until late in the disease, or until after death. There are instances where the victim has died of rabies, yet the infecting dog has recovered. In assessing the length of the period of incubation, apparently well-authenticated cases of rabies may commence as early as ten days after exposure, but hysterical manifestations simulating those due to rabies come on a few hours or days after the assumed exposure. The mental behaviour of the patient during the probationary period may be of assistance in making a diagnosis, but many cases show no disturbance whatever till tell-tale signs develop. The chief difficulty is, of course, with hysterical manifestations, and it is stated that hypersensitiveness to draughts of air, which is common in true rabies, is not produced in hysteria, so that fanning a patient, when unnoticed by him, may produce a convulsive seizure. Tetanus and mania may also simulate rabies. The absence of trismus in one, and of convulsive seizure in the other, will help. Some paralytic cases of rabies may simulate Landry's paralysis.

In the lower animals there are a variety of diseases such as dog distemper, dog hysteria, or brain tumours, which may simulate rabies. Then there is the *pseudo-rabies* or "mad itch" of Aujesky. This virus is much more resistant to desiccation. Remlinger and Bailly find that the intraocular route is the most practical in experimental infections, because in *pseudo-rabies* the issue develops suddenly, which is not the case in true rabies. The infection is transmitted along the axis cylinders of the nerves and reaches the ganglia and segments of the cord, and this degeneration is probably responsible for the itching from which the disease takes its name. Pseudo-rabies has occasionally occurred in men, usually as a result of handling infected animals. It is a non-fatal disease and is characterized by intense itching.

Special mention must be made of the presence of the virus in the lung, and the disease has been reproduced from inoculation of liver, spleen, kidney, testicles, suprarenals, and bone-marrow.

It should be noted that at least two cases of "psychological" rabies have occurred in a medical man and a veterinarian who had been bitten by dogs suspected of having rabies. Apart from psychological symptoms, there were no nervous changes.

Treatment

(*a*) **Treatment of the developed disease.**—No cure has yet been devised for the fully developed disease. In analogy with other virus diseases, a potent antirabic serum has no effect once the symptoms have begun. Therefore fully developed rabies in man must be treated on symptomatic grounds. Chloroform inhalations are given for control of painful spasms; chloral and bromides *per rectum* and, if possible, curare, subcutaneously. Morphia is apt to increase the mental excitement and suffering. Where the patient cannot swallow food, rectal alimentation is probably to be preferred to feeding by the stomach-tube. Intubation or tracheotomy are probably both useless for the relief of dyspnœa and suffocation. Mechanical restraint is generally unnecessary and should not be resorted to except in violent maniacal forms. The attendants must preserve a calm and pleasant demeanour and when speaking of the disease should do all possible to reassure the patient.

(*b*) **Prophylactic treatment of person exposed to infection.**—Cauterization of the infected wound has been practised since time immemorial and, when properly carried out, it is undoubtedly of some benefit, and it has been shown by experiment that the incubation period is prolonged, even when it does not prevent the extension of the infection, and in this manner it allows more time for the establishment of immunity by antirabic inoculations. Actual cautery is very painful and is only efficient if done thoroughly and immediately. The best method is to touch all parts of the wound down to its depths with nitric acid. Carbolic acid is probably less effective.

(*c*) **Preventive inoculation.**—The Pasteur treatment for the prevention of the onset of rabies in exposed persons is designed to confer immunity during the period of incubation. The production of this immunity is necessarily a long process, but fortunately for humanity, the incubation period of rabies is normally much longer.

In those persons in whom, from a combination of factors, the incubation period is a very short one, the Pasteur treatment fails.

The principle upon which the Pasteur treatment is based rests upon the production of immunity by the inoculation of modified rabies virus. This has been finally accomplished by serial passage of the virus through rabbits until a fixed degree of virulence has been reached, and secondly, by the attenuation of this rabbit virus by desiccation.

The first of these processes is the more important and the one most frequently employed at the present time. The following methods have been employed :

(1) *Unmodified fixed virus*, introduced by Ferran. 0·08 grm. of cord of a rabbit dead of a fixed-virus infection is emulsified with the aid of fine sand, using 8 c.c. of salt solution or bouillon ; 6 c.c. of the top fluid are injected subcutaneously into three different parts of the body, 2 c.c. in each. The injections are repeated on five successive days.

(2) *The dilution of fresh-fixed virus*, a method introduced by Högyes, who maintained that the diminution of the virus could be more accurately controlled by simply diluting the fresh virus with salt solution and increasing the dosage as treatment progressed by increasing the strength of the emulsion. An improvement which has been suggested by Harvey and McKendrick is to take smaller amounts of an original emulsion of fixed virus prepared from the spinal cord of a rabbit dead of a fixed-virus infection (or killed), rubbing

it up with sterile salt solution in the proportions of 1 : 100. By appropriate additions, dilutions are prepared varying from 1 : 200 to 1 : 10,000. The dilutions are then used for immunizing. For severe cases, head or face wounds, as many as five injections are given daily in dilutions varying from 1 : 2,000 to 1 : 10,000, in the first four days, and subsequently, to the twentieth day, two to three times daily. Formulæ have to be devised to suit individual cases.

(3) *Fixed virus attenuated by drying.*—The original method of Pasteur, and the one still most extensively practised, has the advantage that it may be administered by private doctors at distances from the laboratory, since dried virus can be preserved by glycerinization and dispatched in this condition. The original scheme of Pasteur for the employment of this method has been greatly modified, according to the time consumed by the treatment, or by dispensing with some of the more attenuated cords, and by increasing or diminishing the dosage given at individual injections. In the first four days two 3 c.c. injections are made daily of emulsions of cord dried *in vacuo* 14, 13, 12, 11, 10, 9, 8, 7 days respectively. The total length of treatment is twenty-one days.

(4) *Fixed virus attenuated by heat.*—A method advocated by Babes appears to be merely a more difficult method of attaining the same end as accomplished by the desiccation method.

(5) *Fixed virus acted on by glycerin.*—While glycerin possesses the power of conserving rabies virus in an active state for a month or more, on prolonged exposure this virulence is lost, although the immunizing power may be retained. This is the method which was advocated by Calmette, although rarely is this immunity sufficiently substantial to withstand subdermal inoculation tests with the fixed virus.

(6) Marie has claimed that a rapid immunity is secured by treating a fixed virus partially neutralized by antirabic serum *in vitro*. It is claimed that in this way a virus of high immunizing power, but of diminished infectious properties, can be administered. For this method one gramme of the bulb of rabbit is taken. A passage-fixed virus is rubbed up with 9 c.c. of veal broth and the emulsion strained through cloth. To 2 c.c. of this emulsion is added 4 c.c. antirabic sheep serum, previously heated for thirty minutes at 56° C. The 6 c.c. of mixture is injected into the skin of the abdomen in two places and the same injections are repeated on three following days.

Formalinized virus grown in tissue-culture virus can confer considerable immunity to mice, while after exposure to ultra-violet light the virus is still antigenic.

(7) The *carbolized fixed virus* is used at Kasauli and other stations in India. The whole brain is removed and a solution containing 1 per cent. of phenol in 0·85-per-cent. salt solution is mixed and placed in a mortar in an incubator at 37° C. for twenty-four hours—sufficient to kill the virus. The suspension is stored at O.C. while tests are being carried out and is used as a vaccine after two to three weeks' storage.

Before inoculation the suspension is again diluted with an equal part of 0·85-per-cent. salt solution, so that it finally contains 0·5 per cent. brain substance. Each patient, however severely bitten, receives 4 c.c. of this suspension for a period of fourteen days.

Serum therapy.—Although when it was first discovered that rabies serum was capable of destroying rabies virus *in vitro* great hopes were entertained regarding its action in man, the results have been disappointing.

The indications for the Pasteur treatment.—All persons who have been bitten by rabid animals, or who have had open wounds or scratches contaminated with the saliva of rabid animals, should receive the treatment. If, however, the animal remains alive and *well* for ten days after administering the bite treatment may safely be discontinued. In persons who have drunk the milk of infected cows, the possibility of infection is very remote, as the gastric juice is destructive to the virus. Everyone who has been bitten by animals presenting symptoms of rabies should receive antirabic treatment, whether or not the suspicion is confirmed by histological examination, and pending the result of inoculation tests. Those persons who are bitten by animals which do not show any of the symptoms of rabies should not be exempt from the necessity for treatment until the biting animal, which should be carefully confined and watched, is shown to be free from the disease. It must be emphasized that histological examination is conclusive only when positive and Negri bodies are demonstrable in the central nervous system.

The results of the Pasteur treatment.—Even under the system of the most rigorous examination of the results of this treatment, it is extremely difficult to determine exactly the mortality-rate after the bite of a rabid dog.

In untreated persons the estimated mortality of statistics very accurately kept is about 14·8 per cent. in 122 persons (Doebert, 1909). As a general statement it may be said that the total mortality of bitten persons subjected to antirabic inoculations is about 1 per cent., of which half could not, on account of the short time permitted for the establishment of immunity, have been expected to live.

Immunization of animals.—In South America cattle in many areas are being immunized prophylactically, while in certain towns dogs have been vaccinated. During the rabies outbreak in Singapore in 1937, arrangements were made to immunize the whole dog population, approximately 13,000, of Singapore Island. A killed virus should preferably be used for the immunization of animals.

Examination of suspected material for evidence of rabies.—The material generally consists of the head of some animal, most frequently the dog, and may be wrapped in cloths soaked in bichloride of mercury or other germicidal solutions, while for miscroscopic examination material may be sent already fixed in weak alcohol. For inoculation the medulla placed in glycerin is suitable. Sections give better results than smears, but naturally take longer to perform. If grossly contaminated with bacteria, the tissues should be treated with ether in a final concentration of 10 per cent., which does not destroy the virus when allowed to act for two hours at 4° C.

In order to locate the hippocampus, or *cornu Ammonis*, the brain is placed upwards, and the temporal lobe lifted outwards from the median line until the cornu comes into line as a long cylindrical whitish body tapering at its enterior end. Smears are made on slides or cover glasses by crushing a small section of brain matter between two of them and drawing them out under gentle pressure to produce a fairly thin film. After fixation they are stained in Unna's polychrome methylene blue for three minutes and, after differentiation in 95 per cent. alcohol, are examined. Negri bodies stained in this way take on a magenta colour. In recent years it has been suggested that the mesencephalon, or oculo-motor nucleus, is a more favourable site than the hippocampus for the demonstration of Negri bodies. Morgan and McKinnon, however, have found that in naturally infected dogs and donkeys, the hippocampus is the site of election.

The other technical methods to be studied are the methods of subdermal inoculation into rabbits, which is performed by a small trephine or jeweller's drill, to effect an opening into the skull large enough to admit a needle. The mouse is more suitable than either the rabbit or the guinea-pig. Negri bodies can be demonstrated in mouse brains eight to nine days after inoculation (Sulkin and Nagle).

For the technical method of removal of the spinal cord from the rabid rabbit and the methods of drying *in vitro*, more authoritative works must be consulted. The present dry method consists of cutting of 1 cm. pieces of cords of rabbits killed each day after inoculation, up to the eighth day, which should be placed immediately in glycerin in a cold place where they will retain their potency for several weeks at the point where it was when they were cut off. Material conserved in this way can be distributed at some distance from the laboratory. It is first cut into half-centimetre pieces, each of which serves, when emulsified in 2½ c.c. of salt solution, for one injection.

CHAPTER XX

DENGUE

Synonyms.—Dandy Fever; Breakbone Fever; Chapenonada (Philippines); Sellar Fever.

Definition.—A specific fever conveyed by *Aëdes ægypti* (*Stegomyia fasciata*) and, possibly, other mosquitoes, occurring usually as a rapidly spreading epidemic. Throughout the febrile stages, and often subsequently, severe rheumatic-like pains are a prominent symptom. The disease in its active form lasts about a week, and is attended with little, if any, mortality. Severe cases closely simulating yellow fever may occur.

Geographical distribution and mode of spread.—Dengue is apt to occur in epidemics, and has appeared in Syria, Asia Minor, on the Ægean shores of Greece and Turkey, in North Queensland, in Charleston and Philadelphia in the United States, and as far south as São Paulo in Brazil. It is endemic in the West Indies, and in Fiji, Samoa, and other Pacific islands. There occurred a very big epidemic in Greece, when in Athens a series of clinical manifestations characteristic of dengue appeared, and it is believed that there were 239,000 cases of dengue up to September, 1928. Dengue occurred in the United States in 1922–23 and then not until 1934.

Epidemiology and endemiology.—The characteristic of dengue fever is that it is apt to recur at intervals of years, sometimes in pandemic waves, during which, it may be, three-fourths of the population are attacked. The epidemic may last for one season or may be spread over several years. Between these epidemics, cases occur sporadically, by which means the virus is maintained and forms the nidus of infection for a new epidemic, but owing to their mild nature they are frequently not recognized. In its pandemic form the disease often appears at a considerable distance beyond its usual confines, and may even ascend mountains to a height of 5,000 feet. The epidemiology appears to be dependent more upon conditions which are suited to the particular mosquito conveying the disease than upon those affecting man. Owing to the shortness of the immunity in man, the control of dengue requires a reduction of the mosquito index to zero.

When dengue spreads beyond its ordinary tropical limits, as for example in the epidemics of Philadelphia and Asia Minor, the extension occurs only during the hottest part of the year—in the late summer and early autumn.

Epidemics occur generally after the rainy season and, in the Pacific islands at any rate, the disease appears to have a seasonal incidence during June, July, and August.

It would appear that dengue prefers the coast-line, the deltas and valleys of great rivers, to the interior of continents. The Grecian epidemic of 1928 was ascribed to the great increase of the population of the city in recent years and the establishment of a large non-immune community increased by a great influx of refugees. There were numerous breeding-places of mosquitoes in the Piræus and it was estimated that 90 per cent. of the population became infected.

Ætiology.—Graham, in Beirut, Syria, first suggested that the disease was transmitted by a mosquito, *Culex fatigans*, and Ashburn and Craig (1907) demonstrated that the disease is caused by a filterable virus which is not contagious, and that a true immunity to reinfection is present in certain individuals.

By a series of well-conceived and carefully-carried-out experiments, Cleland, Bradley, and MacDonald in Australia have proved that the virus of dengue is conveyed by *Aëdes ægypti* (*Stegomyia*), and not by *Culex fatigans*. By subinoculation from one individual to another they transmitted the disease for four generations, and showed that the virus is present in the blood from the second to the fourth day of the disease. Experiments by Siler have confirmed this work. He found that the blood in dengue is infective to the mosquito for eighteen hours *before* onset to the end of the third day of the illness. The mosquito, *A. ægypti*, does not become infective for eleven to fourteen days, but then remains so for the rest of its life. When the temperature is below 18° C. the mosquitoes do not become infective. Passage of the virus through man to the mosquito fails to attenuate or increase it. Simmons (1931) has shown that another species of mosquito, *Aëdes albopictus*, is an efficient carrier of the virus of dengue, and is probably the chief vector in the Philippines. In Florida, it has been suggested on epidemiological grounds that *Aëdes tæniorhynchus* may act as a transmitter.

Blanc and Caminopetros have studied the epidemiology of dengue in Greece and Macedonia, and have been able to show that in these countries the distribution of dengue and of *Aëdes ægypti* correspond, but in Australia the distribution of dengue is always rather less extensive than that of *A. ægypti*. An idea has been fostered that some correlation between the virus of dengue and that of yellow fever might exist. This suggestion has received no confirmation from the work of Stefanopoulo and others who tested the sera of several individuals who had suffered from dengue by the yellow-fever mouse-protection test. Moreover, Dinger and Snijders fed mosquitoes (*Aëdes albopictus*) on dengue cases in Medan, Sumatra, and then dispatched them by ship to Amsterdam, where they were re-fed on volunteers who in every case subsequently developed dengue. It was thereby proved that the same virus in the same batch of mosquitoes produced different types

of fever in different individuals. One case might show the typical saddle-back temperature curves; another, continuous fever lasting seven days, and from this is drawn the obvious conclusion that the five-day fever of Scheer and the seven-day fever of Rogers, are not distinct diseases.

Manoussakis has shown that the dengue virus can be transmitted almost indefinitely from one volunteer to another without alteration in virulence. In each case the incubation period of the disease was five to seven days. Twenty-five c.c. of blood are taken from a dengue case in the first twenty-four hours of the disease, placed in 200 c.c. of normal saline, sealed and placed in the incubator; after six days' incubation 6 c.c. of the supernatent fluid, injected subcutaneously into volunteers, gave rise to the disease. The virus can be dried and frozen without losing its virulence. This was shown by Hoffmann, Mertens and Snijders, who transported the dried serum from Java to Amsterdam and inoculated volunteers with it, reproducing typical fever 285 days after it had been abstracted from dengue fever cases.

The disease can be transmitted from man to various species of monkey. In *Macaca mulatta* there is, as a rule, only a leucopenia with reduction in the number of polymorphonuclear leucocytes, but the virus is present in the blood; the disease cannot be transmitted from monkey to monkey. Mice are not susceptible to inoculation. The so-called dengue of cattle, more correctly termed three-days or ephemeral fever, though due to a virus, has no relation to human dengue.

Pathology.—On account of the low mortality, post-mortem records are few. In the autopsies recorded, localized pulmonary and intracranial inflammation were the special features. Serous effusions in the neighbourhood of joints and inflammation of the crucial ligament of the knee have also been noted, while myocarditis, nephritic lesions with degeneration of the cells of the convoluted tubules, and a true encephalitis with leucocyte blocking of some of the cerebral capillaries, have also been recorded.

Symptoms.—The *incubation period* seems to be somewhat variable, generally from five to nine days, though sometimes it appears to be less. The course of the disease may be divided into three periods: the stage of invasion, lasting two to three days; the stage of remission, lasting twelve hours to three days; the terminal fever and eruption.

Stage of invasion.—An attack of dengue may be preceded for a few hours by a feeling of malaise or, perhaps, by painful rheumatic-like twinges in a limb, toe, finger, or joint, which when confined to the knee-joint are excruciating. Usually it sets in quite suddenly. Sometimes the fever is ushered in by a feeling of chilliness or even by a smart rigor; sometimes a deep flushing of the face is the first sign of the disease. However introduced, the fever rapidly increases. The head and eyeballs ache excessively, and some limb or joint, or even the whole body, is racked with peculiar stiff, rheumatic-like pains,

which, as the patient soon discovers, are very much aggravated by movement. The loins are the seat of great discomfort, amounting in some cases to actual pain; the face—particularly the lower part of the forehead, round the eyes, and over the malar bones—may become suffused a deep purple; and often the skin over part or the whole of the body, and all visible mucous surfaces, are more or less flushed; those of the mouth and throat being sore from congestion and perhaps from small superficial erosions. The eyes are usually much injected: very often the whole face is bloated and swollen. This congested, hypersensitive, and erythematous state of the skin constitutes the so-called prodromal eruption. There may be a *tache cérébrale.*

These symptoms becoming in severe cases rapidly intensified, the patient, in a few hours, is completely prostrated. His pulse has risen to 120 or over; his temperature to 103° F. (Chart 19), in some cases to 105°, or even to 106°. He is unable to move owing to the intense headache, the severe pain in limbs and loins, and the profound sense of febrile prostration. From time to time the skin may be moistened by an abortive perspiration, but for the most part it is hot and dry. Gastric oppression is apt to be urgent, and vomiting may occur. Gradually the tongue acquires a moist, creamy fur, which, as the fever progresses, tends to become dry and yellow. In this condition the patient may continue for from one to three or four days, the fever declining somewhat after the first day.

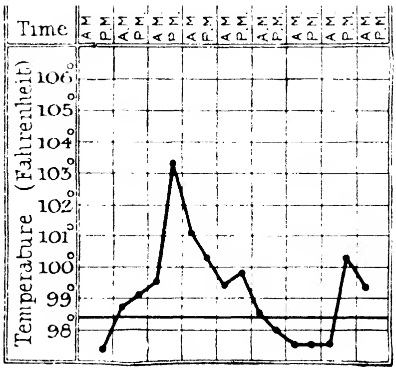


Chart 19.—Dengue. *After Cleland and Bradley.*)

In a proportion of cases, and particularly in certain epidemics, crisis does not occur, the fever slowly declining during a period of three or four days.

Stage of remission.—When the second stage is established and the thermometer has sunk to normal, the patient is sufficiently well to leave his bed and even to attend to business. The tongue clears, and the appetite and sense of well-being return to some extent.

Terminal fever and eruption.—The state of comparatively good health continues to the fourth, fifth, sixth or even to the seventh day, counting from the onset of the illness. Then there is generally a return of fever, slight in most cases, more severe in others. With the recurrence of the fever an eruption of a rubeolar character, consisting of dark, dusky spots, appears. The pains likewise return, perhaps in more than their original severity. Though the fever

subsides in a few hours, the eruption, at times very evanescent, may keep out for two or three days longer, to be followed very generally by an imperfect furfuraceous desquamation.

Characters of the eruption.—The terminal eruption of dengue possesses very definite characters. It is absent in a very few cases, but in many, being slight, it is overlooked. Usually it commences on the palms and backs of the hands, extending for a short distance up the forearms. It quickly extends, and is best seen on the back, chest, upper arms (Plate VIII, Fig. 2), and thighs. Here it appears at first as isolated, slightly elevated, circular, reddish-brown, rubeoloid spots, $\frac{1}{8}$ to $\frac{1}{2}$ in. in diameter, thickly scattered over the surface, each spot being isolated and surrounded by sound skin. There may be a general coalescence of spots, isolating here and there patches of sound skin; in this case the islands of sound skin give rise, at first sight, to the impression that they constitute the eruption—a pale eruption, as it were, on a scarlet ground, giving an appearance of a condition "midway between scarlet fever and measles." The spots disappear on pressure, and never, or rarely, become petechial. They fade in the order in which they appear—first on the wrist and hands; then on the neck, face, thighs, and body; last, on the legs and feet, but may still be visible for three weeks after recovery from the fever.

Desquamation may go on for two or three weeks. In many it is trifling in amount; for the most part it is furfuraceous.

At this stage the characteristic slowing of the pulse, which may fall as low as 44 per minute, and the leucopenia, which may fall as low as 1,200 leucocytes, are noted; the latter is due to a marked decrease of the polymorphonuclear cells, which may be reduced to 40 per cent., and to a relative increase of the lymphocytes.

Rheumatoid pains persist for some time after convalescence has been established. They are usually worse on getting out of bed in the morning and on moving the affected part after it has been at rest for some time; they are relieved somewhat by rest and warmth. In some cases a periarthritis of the knee- or ankle-joint, which may cause considerable disablement, does not clear up for several months. Dengue pains remain in the small muscles of the hands and soles of the feet, probably located to the deep fascia. These pains in the feet eventually wear off on walking.

Convalescence may be very much delayed by anorexia, general debility, mental depression, sleeplessness, evanescent feverish attacks, boils, and urticarial, lichenoid, and papular eruptions.

In Europeans an attack of dengue very often leads to a condition of debility, necessitating temporary change of climate, or even return to Europe.

Variability of epidemic type.—Judging from the published descriptions, there is considerable variety in the symptoms of this disease in different places and in different epidemics. Some authors mention

swelling and redness of one or more joints as a common and prominent symptom ; others refer to metastasis of the pains, enlargement of submaxillary glands, orchitis, mental depression, hæmorrhages, and so forth, as being frequently present. However this may be, the essential symptoms in well-marked cases are the same practically everywhere and in all epidemics, viz. suddenness of the rise of temperature, an initial stage of skin congestion, limb and joint pains, and a terminal rubeoloid eruption.

In the comparatively recent Athens epidemic, it is stated, some of the following clinical manifestations were noted : Gastro-intestinal disturbance, vomiting, epigastric pain, hiccough, hæmorrhage into skin and mucosa, and complications such as parotitis, otitis, furunculosis, and broncho-pneumonia. In some acute cases with early and severe gastro-intestinal phenomena, bleeding from the gums and haematemesis was noted. True encephalitic symptoms have also been described.

Relapses are not uncommon in dengue, and second and even third attacks during the same epidemic have been recorded. As a rule, however, susceptibility to the disease is exhausted by one attack.

Immunity.—Schule pointed out that certain of his volunteer American soldiers proved remarkably resistant to experimental inoculation with the dengue virus, and these were individuals who had for some time been resident in an epidemic area of the disease, and probably this immunity is due to previous mild attacks of the fever. The immunity in dengue does not last more than six months ; it thus differs from that of yellow fever, which is life-long.

Mortality.—In uncomplicated dengue the mortality may be said to be almost nil (0·1 per cent., Hare). During the 1928 epidemic in Greece, Cardamitis gave the mortality-rate as 1 : 61,000.

Diagnosis.—Dengue must not be confounded with yellow fever, Rift Valley fever, rötheln, scarlatina, measles, syphilitic roseola, influenza, cerebro-spinal meningitis, typhus, hæmorrhagic smallpox, enteric, phlebotomus fever, seven-day fever (leptospirosis), rheumatic or malarial fever. A knowledge of the distinctive features of these diseases, and the fact that dengue is attended with a rash and with articular pains, and that it occurs in great and rapidly spreading epidemics, should prevent any serious error in diagnosis.

Treatment.—Were it possible to secure perfect isolation and immunity from mosquito-bite for the individual during an epidemic of dengue, doubtless he would escape the disease. Even comparative isolation is attended with diminished liability.

Like the allied fevers, dengue runs a definite course ; therefore it is useless to attempt to cut it short. The patient should go to bed as soon as he feels ill, and should keep his room till the terminal eruption has quite disappeared and he feels well again. Ten days is not too long to allow in severe attacks. As in influenza, light liquid

diet, rest, and the avoidance of chill conduce powerfully to a speedy and sound convalescence. At the outset of the fever some saline diaphoretic mixture, with aconite, may be prescribed with advantage. If the pains be severe and the fever high, antipyrin, or phenacetin, belladonna, or vinum colchici (15 min. t.d.s.), give great relief. Cold applications to the head are comforting. If the temperature rises to 105° F. or over, cold sponging or the cold bath ought to be resorted to. If the pains continue very distressing, a hypodermic injection of a minute dose ($\frac{1}{10}$ gr.) of morphia will afford welcome relief and do no harm. Purgatives and emetics should be avoided unless pronounced constipation, or a history of surfeit, urgently demands their exhibition. In the Athens outbreak urotropine in full doses was given in the early stages, and if pains were severe, aspirin, pyramidon, and caffeine. For cerebral symptoms, which in some patients might be an important feature, bromides and strophanthus are indicated. The pain caused by the muscular movements entailed by the efficient action of purgatives more than counterbalances any advantage the latter might otherwise bring. Wine in the early stage is not advisable. Freshly-made lemonade, or iced water, will be found an acceptable drink during the fever.

For the pains experienced during convalescence, rubbing with opium or belladonna liniment, gentle massage, electricity, salicylates, small doses of iodide of potassium, have been advocated. Debility, or anorexia, indicates tonics, such as quinine, strychnine, mineral acids, or vegetable bitters, and change of air.

Prophylaxis is the same as for yellow fever and for other mosquito-borne diseases, and is directed against infected mosquitoes.

Prophylactic inoculation.—St. John and Holt attempted to produce a dengue vaccine. This vaccine from the liver and spleen of dengue-infected monkeys did not protect volunteers from an attack of dengue : but there was evidence that these attacks in the inoculated were very mild ones. The possibility of producing an attenuated tissue-culture virus vaccine should be considered.

CHAPTER XXI

PHLEBOTOMUS FEVER

Synonyms.—Papataci Fever; Three-day Fever; Sandfly Fever, "Dog Disease."

Definition.—A specific fever of short duration and no mortality caused by a virus introduced by the bite of the sandfly (*Phlebotomus*).

History.—This disease has been recognized clinically for upwards of a century, and described under a variety of local names; but its definite relation to its transmitting agent, although suspected by McCarrison in Chitral in 1903, was not established till 1908, when Doerr published his observations, since confirmed by Kilroy, on the infectivity of the blood in this form of fever and the rôle of the sandfly as transmitter. Whittingham has described minutely the various stages in the life-history of the phlebotomus, and has succeeded in rearing these insects in captivity.

Geographical and seasonal distribution.—The range of phlebotomus fever is probably coextensive with that of the insect transmitter. In the tropics it may break out at any time as an epidemic amongst new arrivals; in the subtropics it occurs only or principally during the summer and early autumn. Natives of the endemic area appear to be immune. Where the phlebotomus is absent, e.g. Bermuda, this fever is not found. In some phlebotomus-haunted places as many as 50 per cent. of new-comers are attacked. This fever was much in evidence during the Great War, in Gallipoli, Salonika, the Ægean Islands, Egypt, Palestine, Syria, Iraq, and India, but there is no record of its occurrence among troops in East Africa. Widely distributed in Africa and Asia, sandfly fever is found in the Caucasus, Chitral, and the Himalayas, up to a height of 4,000 feet. In the New World it has recently been found in Northern Argentina.

Ætiology.—The germ resides in the patient's blood during the first two days of the fever. It is ultramicroscopic, passing through filters which arrest *Brucella melitensis*. According to Doerr, the virus is transmitted hereditarily through the egg and larva of phlebotomus to the imago; this, however, has not been firmly established. A short sharp fever has been produced in monkeys after intravenous injection of sandfly-fever blood. In Egypt, it is said, a similar fever exists in cattle, but it is doubtful whether three-day fever of cattle,

also called dengue of cattle, has any relation to sandfly fever. Little is as yet known in regard to the physical properties of the virus. According to Whittingham, the virus may survive the winter, either free in the soil, or within the bodies of plebotomus larvæ which inhabit such sites as moist soil and porous walls. The larva is thought to extract the virus in feeding upon the fæces of the adult fly; but Moshkovsky and his colleagues in Moscow have recently shown that the virus may be transmitted by the female Phlebotomus to the egg and so to the larva. This is the only instance in which an animal virus has been transmitted hereditarily by an insect vector. This may be an important epidemiological consideration and may explain the suddenness and extent of outbreaks of sandfly-fever in the Indian frontier in the spring months. In one case, infection followed the bites of female sandflies that had just hatched, thus disproving the suggestion that the virus is only transmitted after the sandfly has already digested a meal of blood.

Shortt, Poole and Stephens have shown that, as with dengue, the sandfly-fever virus can pass through L_3 and L_5 Chamberland filters, and that the virus is present in the blood during the first and second day of the disease. They proved that it can survive outside the body for sixty hours.

Representatives of the genus *Phlebotomus* are to be found in most tropical and subtropical countries. The various species are usually designated "sandflies." They are exceedingly minute, very delicate greyish, or brownish, somewhat slenderly-built insects that bite principally during the night and that can pass easily through the meshes of an ordinary mosquito-net. The powers of flight are feeble; more usually the insects progress by a series of short skips.

P. papatasii, the species on which Doerr's observations were made (hence one of the names for the disease, papataci fever), lays about forty eggs selecting for the purpose damp localities such as the walls of cellars, of latrines, cesspools, crevices in walls, caves, and embankments. The cycle of egg, larva, and imago takes about one month in warm and upwards of two months in cooler weather (*see* pp. 997–1,000).

There has been much confusion in the nomenclature of the various species of *Phlebotomus*, and it has not been determined which of them, other than *P. papatasii*, conveys the infection. The insect can transmit the infection after an incubation period of six days.

Pathology.—Dengue and phlebotomus fever have several important points in common, a circumstance suggestive of the possibility of a common or, at all events, a similar origin. Each is transmitted by an insect; their germs occur in the blood-stream and are filterable; they are diseases of warm climates only; and clinically, they are characterized by a short incubation period and a brief and rapidly developed fever which is usually associated with relatively slow pulse and leucopenia, and relative decrease of the polynuclears. There is no evidence that these diseases are mutually protective.

Symptoms.—The bites of the sandfly occasion a considerable amount of irritation, resulting in hyperæmia and even in œdema.

After an incubation period of from four to seven days, with or without a prodromal stage, the fever is ushered in suddenly by slight or more severe rigor. The face becomes flushed and swollen, frontal headache is intense, and there is usually severe general aching and stiffness in the back of the neck. Pain at the back of the eyes, accentuated by pressure on the globes or by the least movement of the head, is characteristic. Supraorbital headache is also quite common. There are influenzal pains in the back and legs and general stiffness of the muscles—more rarely the pain is referred to the epigastrium. The patient is drowsy, but suffers from insomnia. The conjunctivæ are

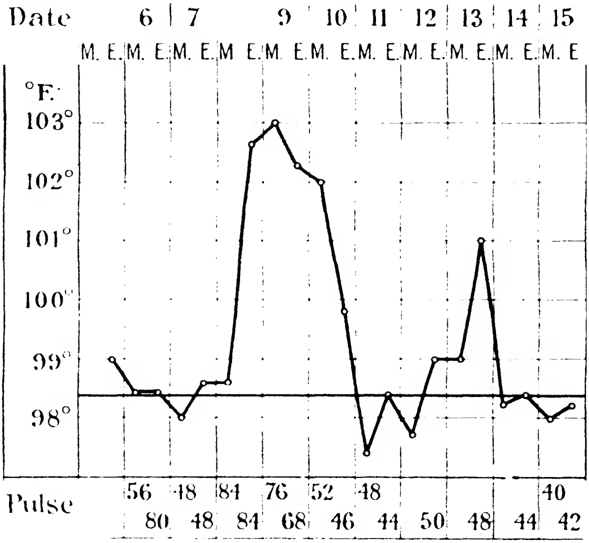


Chart 20.—Phlebotomus fever showing prodromal period, typical attack, recrudescence and bradycardia. (*Lambert, Jl. Roy. Nav. Med. Ser.*)

so injected that they have been likened to those of a mastiff. The tongue has a central fur. The fauces and palate are often congested, and are studded with small vesicles. In from twenty-four to thirty-six hours the temperature has reached 103–104° F. (Chart 20). It keeps about this point for a day longer, and then begins to fall, with or without epistaxis, vomiting, sweating, diarrhœa, reaching the normal about the end of the third or beginning of the fourth day. The patient continues debilitated, especially mentally, for a week or two longer. According to Lambert, the name "three-day fever," as applied to the disease, is quite misleading, since the pyrexial period may occasionally vary from two to eight days.

The blood-picture shows a slight leucopenia without serious

alteration in the number of mononuclears. The pulse-rate is relatively slow. Bradycardia is noticeable by the second day of the disease, as soon as the patient complains of headache.

No serious complications occur, but in some years diarrhœa, in other years pharyngitis, is a feature of the epidemic. Constipation, vomiting and stiffness of the muscles at the back of the neck, are not uncommon symptoms. An attack would seem to confer a certain amount of immunity, though second attacks are by no means uncommon, but are milder than the primary ones. Shortt has proved that a certain degree of immunity is produced and persists for one year after an attack.

Le Gac and Albrand have found that the cerebro-spinal fluid is under increased pressure and shows from 10 to 20 lymphocytes per cu.mm. Albumin is always increased and the chlorides slightly decreased.

There are no important sequelæ, save that the debility which ensues in some individuals is quite out of proportion to the intensity and duration of the initial attack. The mortality is nil.

Diagnosis.—It is extremely difficult in the early stages to distinguish this fever on clinical grounds from malaria (especially subtertian), from paratyphoid, dengue, typhus, and influenza. In typhus the greater hebetude, and in influenza the respiratory catarrh, must be taken into consideration.

Treatment.—The most valuable drug in the treatment of sandfly fever is opium; 30 drops of the liquor opii sedativus may be given at the onset. It greatly relieves the headache. Quinine is useless. Tincture of iodine should be applied to the bite. The headache has been relieved by lumbar puncture.

Prophylaxis.—As it would appear that phlebotomus fever is a disease of locality, houses and places believed to be infected should be avoided and, where possible, disinfected.

With a view to diminishing the local sandfly pest, all rubbish should be burned or otherwise got rid of; ruinous walls demolished, the cracks in walls filled in with tar or mortar, latrines smoked with sulphur fumes and put into sanitary condition, and dark damp places dried, whitewashed, and ventilated. No gardens or cultivated ground should be permitted in the immediate vicinity of buildings, and creepers should not be allowed to grow on barrack walls. The adult flies can be killed in numbers by "swatting." By these and similar measures much can be done to control the infection. Unfortunately, a mosquito-net having a mesh sufficiently small (i.e. 45 holes to the inch) to keep out sandflies is intolerable to a white man in a hot climate. As the phlebotomus does not fly higher than 10 ft., the removal of inmates to an upper story is a very effectual preventive measure. It is said that a lump of camphor placed in the bed repels the insects. Of the repellent ointments in use for application to the skin, the following is considered the most efficacious (Balfour):

℞ Ol. anis.	} āā ♏iii	(0·18 c.c.)
Ol. eucalypt.		
Ol. terebinth.		
Lanolin.	℥i	(31·1 grm.)

Choyce recommended 5-per-cent. thymol made up with firm wax into a candle and rubbed into the skin, where it forms an oleaginous covering, as an excellent general prophylactic measure.

In the British Army in Egypt and in India the official antimosquito cream described at page 134 is considered most effective, and least disagreeable as a repellent (Manifold). It should be smeared on the face, hands, and other exposed parts.

To reduce the incidence of sandfly-bites general measures should be instituted. Shorts should not be worn after sundown, wrists and ankles should be smeared either with the above ointment, or with "vermijelli," or oil of citronella. Wellington boots worn after dusk afford a good protection to legs and ankles.

Air-currents have a marked effect on sandflies, and Whittingham has shown that the most effective way of ridding quarters of these pests is to create a strong current by means of electric fans.

CHAPTER XXII

THE POCK DISEASES

At the present time the classical type of smallpox is confined almost entirely to tropical and subtropical countries, where the preventive measures responsible for the decline of this disease in temperate climates are more difficult to carry out. In British India, for example, the number of cases of variola reported during the year 1938 was 82,640 with a mortality of 27 per cent. During the same period there were severe outbreaks in China (Hong Kong and Shanghai) and in Nigeria ; and a mild form of the disease with no fatalities was prevalent in the southern states of the United States.

During the last few years much has been learnt about the nature and properties of the causal agents of the pock diseases. The greater part of this work has been carried out with vaccinia, and it is therefore necessary to define at the outset the relationship between this virus and variola. That smallpox and all the animal pock diseases are closely related is certain. Vaccinia may be regarded as the virus in its original form from which the more complex viruses, including human variola, have evolved and to which they revert when passed through the cow or calf. Variola virus has also been converted into an attenuated form by inoculating human infective material into monkeys and then inoculating filtrates obtained from the monkey lesions intratesticularly into rabbits. After a number of passages in the rabbit testis the virus is able to produce a confluent eruption when rubbed into the freshly-shaved skin of these animals. This strain of virus is indistinguishable from the classical strains of vaccinia which were obtained by passage through calves of human smallpox, or naturally occurring cowpox. The transition from variola to vaccinia is, fortunately, not reversible, so that once a strain of virus has been adapted to the calf or sheep it can be inoculated into man, producing in him a mild illness which renders him subsequently immune to the virulent form, smallpox. On rare occasions vaccination gives rise to a generalized papular or vesicular eruption with severe constitutional symptoms which may terminate fatally. This condition is believed to be due to an abnormal susceptibility to vaccinia, and not to an increase in virulence of the virus.

Nature and properties of the causal agent.—The infective agent of vaccinia is a spherical body, measuring about 0·17 μ in diameter, to which the noncommittal term "elementary body" is

applied pending the settlement by further research of the much-disputed question whether viruses should be regarded as micro-organisms or macro-molecules. These bodies were first seen and described in 1887 by Dr. John Buist of Edinburgh, who found them in the vesicle fluid of smallpox and vaccinia. In 1906 they were rediscovered by Paschen and are frequently referred to in the literature as "Paschen bodies." It is only during the last few years, however, that the bodies have been proved to be the causal agents. Methods have now been evolved of preparing pure suspensions of the elementary bodies from the skin lesions produced in rabbits and sheep by specially-selected strains of vaccinia virus. These pure suspensions have been employed in recent studies of the physical, chemical and biological properties of the virus, and they are also being used experimentally in place of crude lymph for prophylactic immunization against smallpox. Chemical analysis has shown that the elementary body is composed mainly of nucleo-protein together with a carbohydrate and a lipoid fraction. Highly-purified suspensions of the elementary bodies contain phosphatase and catalase, and these enzymes are believed to be inherent in the virus: no dehydrogenase activity has been demonstrated. Sedimentation photographs of elementary body suspensions, obtained with the Svedberg centrifuge, show fairly well-defined boundaries, indicating that the variation in size of the particles is very small. The bodies have an unusually high charge and electrophoretic mobility; they are also exceptionally sensitive to flocculation by salts. Although their size is below the limit of optical resolution for visible light, they can readily be seen with the dark-ground microscope.

When inoculated by inunction into the skin, the elementary bodies penetrate the cytoplasm of the epidermal cells and there proceed to increase in number, thus producing, perhaps with the addition of material derived from the infected cell, the so-called acidophil inclusion body which was described long ago by Guarnieri. The presence of the virus within the cells causes the latter to increase in size and also to proliferate freely. This increase in thickness of the epidermis together with œdema and by hyperæmia of the subjacent dermis is responsible for the papule. Later, the cells forming the centre of the papule degenerate and liquify, thus producing the characteristic vesicle, in the fluid contents of which the elementary bodies are found in enormous numbers. The vesicle is rapidly converted into a pustule by the immigration of inflammatory cells, mainly polymorphs, derived from the dermis. The fluid provides an excellent culture medium for staphylococci and other organisms and the leucocytic response is largely due to this secondary infection. In non-fatal cases the crusts or scabs which separate after the pustule has dried contain active virus. The high infectivity of smallpox, however, is probably not due to dissemination of the crusts but to lesions present in the mouth, throat and lungs. The expired air of patients suffering from variola has been shown experimentally to contain elementary bodies. The air

in the vicinity of the patient thus becomes charged with microscopic droplets of water which he has exhaled. These droplets evaporate leaving the elementary bodies suspended in the air where, being so minute, they may remain for long periods. A susceptible person breathing such contaminated air becomes readily infected. Contact with fomites is undoubtedly responsible for some infections, but the epidemiological characters of the disease can only be fully explained by the assumption that the virus is air-borne.

Vaccination and variola, in common with other viruses, cannot be cultivated in the absence of living susceptible cells. The virus can be grown readily in tissue cultures of rabbit testis or corneal epithelium and proliferation also takes place in a fluid medium consisting of rabbit serum and Tyrode's solution to which small amounts of minced rabbit kidney or testis have been added. Vaccinia also grows without difficulty when it is implanted on the chorio-allantoic membrane of the developing chick embryo. Both of these methods have been used successfully as a means of procuring a supply of bacteria-free virus material for prophylactic immunization. This culture virus may be inoculated by scarification in the usual way or it may be injected intracutaneously. The latter method has the advantage of leaving no scar but since a vaccination scar is the one infallible sign that a person has been immunized against smallpox, it would increase the difficulties of controlling an epidemic, especially among coloured races. There is evidence that strains which have been grown *in vitro*, or on the egg membrane for a long time, become attenuated so that they may fail to induce a good immunity when inoculated into man. Generalized vaccinia has been known to occur as the result of vaccination with virus grown on the chick embryo.

Laboratory diagnosis.—Elementary bodies can readily be demonstrated in the vesicle fluid by means of the dark-ground microscope. The technique is the same as that used for the detection of spirochætes. Permanent preparations are best prepared by using Gutstein's method :

Solutions needed.—(*a*) 1-per-cent. methyl violet in distilled water.
(*b*) 2-per-cent. $NaHCO_3$.

Technique.—A drop of the vesicle fluid is spread on a perfectly clean microscopic slide in the manner used for making a blood film. Dry films in the air or in an incubator. Rinse the film in physiological saline and then with distilled water. Dry. Fix film in methyl alcohol (or ethyl alcohol) for half an hour or more. Place slide in a dry Petri dish. Mix equal parts of solutions (*a*) and (*b*) in a test tube, filter at once on to slide, cover dish with lid and incubate at 37° C. for twenty to thirty minutes. Rinse in distilled water, dry and mount in cedar-wood oil or liquid paraffin. The elementary bodies are stained distinctly and intensely a light violet colour.

The finding of elementary bodies in the vesicle fluid is of no value

in differentiating smallpox from varicella since the infective agent of the latter disease also takes the form of elementary bodies and the two viruses are indistinguishable under the microscope.

The best known method for the serological diagnosis of smallpox is that of Gordon, Craigie and Tulloch. The pocks are lightly scraped with a scalpel and the material so obtained is suspended in saline. The suspension is clarified by light centrifugation and then mixed with a series of dilutions of rabbit anti-vaccinial serum. The tubes are incubated at 37° C. A positive reaction is marked by the appearance of a finely-floccular precipitate. The reaction is specific for variola and vaccinia ; it is probably a mixed precipitation and agglutination. Diagnosis may also be made by the complement-fixation test, using a suspension of the crusts as antigen.

The serum of a patient who is recovering from an attack of smallpox contains agglutinins which react specifically with variola elementary bodies. These antibodies are not present in detectable amounts until the second week of the disease, and the reaction is therefore of little diagnostic value.

Serological methods have so far failed to discover any antigenic difference between variola major and variola minor. It is thus evident that the diagnosis of smallpox must be made mainly by clinical methods but that laboratory tests may be of use in doubtful cases.

A Note on the Treatment of Variola

The mortality from smallpox, excluding the severe toxic and haemorrhagic forms of the disease, is largely due to secondary pyogenic infection of the respiratory tract. Energetic measures to combat this secondary infection should be commenced at an early stage. In sulphanilamide we now possess a highly-effective chemotherapeutic agent against streptococcal infections, and this form of treatment should prove of great value in smallpox. The use of sulphanilamide, however, is not without danger on account of its toxic properties, and its administration to patients who are already seriously ill would have to be undertaken with caution. Clinical reports on the value of the drug in the treatment of smallpox are, in a limited number of cases, favourable. Drug treatment should possibly be combined with the injection of large doses of concentrated multivalent antistreptococcal serum.

The treatment of smallpox by potent antivaccinial serum has as yet not received the attention which it appears to deserve. Such treatment would need to be given early, since the secondary fever and its attendant dangers would obviously not be influenced by it. Anti-vaccinial serum of high potency can be prepared by immunization of the horse, and it can be concentrated by the usual methods of serum-protein fractionation.

ALASTRIM

Synonyms.—Amaas; Kaffir Milkpox; West Indian Modified Smallpox; Parasmallpox: Variola minor.

Definition.—This disease has been noted by many writers as occurring in the West Indies and South Africa.

The name is derived from the Spanish *alaster,* meaning to scatter or strew over (referring to the distribution of the rash). It is a disease of little or no mortality, and resembles smallpox in its most mitigated form. Indeed, the individual case of this disease is clinically identical with a mild case of smallpox; the diseases can only be distinguished one from the other in the mass.

Geographical distribution.—The disease has been recorded from the West Indies, South and Central America (especially Brazil). Africa, the Mediterranean area, and during the last 20 years from time to time in Great Britain. The most noteworthy epidemic was the one which occurred in Trinidad in 1902.

Epidemiology.—A striking difference between classical smallpox and alastrim is seen in the rate of progress through an unvaccinated community. Smallpox becomes rapidly epidemic, whereas alastrim can only be said to "smoulder," alternately waxing and waning, but never attaining really epidemic proportions. This, no doubt, depends upon the infectivity of the two viruses. There appears to be no seasonal incidence.

The spread of alastrim is brought about by intimate contact and overcrowding.

Ætiology.—Alastrim is very infectious to man, and attacks both sexes: no racial immunity has been observed. The causative organism has not been discovered, though Guarnieri bodies have been described from the lesions (*see* p. 410). The virus is infective under experimental conditions for monkeys and calves, and produces lesions when inoculated into the cornea of rabbits. The crusts off the pocks are believed to convey the virus of the disease. The infectious agent probably resides in the nasal and buccal secretions at an early stage of the disease. Vaccination is protective against alastrim in a very high degree. This, and the fact that two attacks may occur in the same individual, are common both to alastrim and to smallpox.

Pathology.—The lesions are present on the buccal mucous membrane, as well as on the skin, and may extend from the palate down the trachea into the bronchi. The actual pocks appear to involve the skin tissues to a degree intermediate between those of chickenpox and smallpox; they rarely leave any scarring behind.

Symptoms.—The *incubation period* averages about fourteen days; prodromal symptoms may or may not be present. When observed, they are those of an influenza headache, with generalized aches and pains. Severe headache, vomiting, and rigors, typical of the onset of smallpox, are rarely noted. The eruption commences usually on

the third or fourth day, but in some cases there is a complete intermission of all symptoms, during which the patient may return to his duties under the impression that he has recovered from an attack of influenza ; after the lapse of the quiescent period the eruption appears first on the face and palate, then on the hands and arms, and later on the lower extremities. Thus, in these cases there is a prodromal period of seven or eight days.

Individual lesions.—The papules can be palpated under the skin even before they are visible. As a rule, the eruption appears in one crop, and closely resembles that of smallpox in every respect, any differences being due to the more superficial situation of the pathological process in the skin. The pock may be umbilicated, but collapses more completely on being punctured than does the smallpox pustule, that is to say, it is less definitely multilocular. Drying or crusting begins at about the end of the first week. and crusts have usually fallen by the end of the second or third, at which period the patient is considered to be free from infection.

The rash naturally differs somewhat in appearance (*see* Plate X), when it occurs on a dark skin ; the individual pustules, when ripe and full of pus, show as light creamy-coloured areas, in contrast to the dark purple of the surrounding inflammatory zone, and appear as pearls upon a dark background.

Distribution of the eruption.—This is identical with the distribution of the smallpox eruption, which is centrifugal, and it at once serves to distinguish alastrim from chickenpox, the rash of which has a centripetal distribution.

As in smallpox, the most protected parts of the skin are most free from eruptions, i.e. axillæ, groins, and abdomen. The parts most affected are the face, scalp, shoulders, back, arms, and legs. Any part which has previously been especially exposed to irritation is more profusely affected ; thus pocks are apt to cluster at the site of old burns or scars (Plate X).

Confluent rashes may occur, but, though the appearance of the patient is somewhat alarming, his general health appears to be but little disturbed. These cases may be associated with a considerable degree of fever.

It has been noted by most writers on this subject that the fetor accompanying the rash of true smallpox is not present in alastrim.

Prodromal rashes are absent.

The mortality-rate is a minimal one ; in the series recorded it is about 0·45 per cent. (Ribas and Moody).

Treatment is symptomatic only ; patients should be isolated in a smallpox hospital or elsewhere.

Prophylaxis.—Vaccination offers the most efficient method of protection against this disease, as in smallpox. In spite of the mildness of alastrim, it is considered desirable at present to treat it as a form of smallpox, and not only to isolate patients but to vaccinate contacts.

Subsection F—FEVERS DUE TO ATMOSPHERIC CAUSES

CHAPTER XXIII

HEAT-STROKE AND SUN-STROKE

Preliminary.—Leonard Hill states that in hard muscular work the heat production is great and, when well trained, a man does not burn more than one-third of the energy consumed into work, two-thirds going into heat. An ill-trained man, on the other hand, has an efficiency no higher than a steam-engine, and converts 10–15 per cent. of food energy into mechanical work and wastes the remainder in the form of heat. Sweat cools the body by evaporation and every gramme of water takes up some 582 calories of heat in turning it into vapour.

Jones and Mankin, in their studies on submarine ventilation in tropical waters, found that during long submerged runs with high atmospheric temperatures and a high relative humidity, those men who used electric fans suffered no discomfort, whilst those who were some distance removed were distinctly uncomfortable, showing the beneficial effect of removing the envelope of moist warm air from the body and aiding evaporation.

C. J. Martin, in his work on heat regulation in man, found that the mechanism is essentially an "adjustable insulation." A comfortably clothed individual, sitting in a room at 15° C. at 50 per cent. of relative humidity, loses 44 per cent. of excessive heat by radiation, 31 per cent. by convection, and 20 per cent. by evaporation of moisture from the lungs and skin. A resting man produces some 1.2 large calories of heat per minute, which, if lost by evaporation of moisture, must entail a loss from the body of at least 2 c.c. of water per minute. Strenuous work necessitates the evaporation of approximately one pint of moisture per hour, and there must be a corresponding intake of water by the individual.

F. Marsh (1930) finds that in experiments on man complete saturation with water vapour, if the surrounding air is at a temperature of 90° F., causes an immediate and uncontrollable rise of body-temperature. Pembry (1926) has recorded the case of a man born without sweat-glands but otherwise healthy: owing to abnormal rise in his temperature he was unable to do muscular work in summer in England unless his shirt had previously been soaked in water. People with ichthyosis are well known to be intolerant of tropical temperatures.

And thus it comes about that a normal man treated with atropine in therapeutic doses is easily reduced to the same condition as a man born without sweat-glands. Fatigue of the sweat-glands (Haldane) may be due to the low concentration of salt in the blood and to a consequent reduction of the blood volume by abstraction of fluid. A normal man of 60 kilos holds in his body no less than 40 kilos of water, of which about four are in the blood, and if water is slowly abstracted from the blood, it is replaced almost at once from the tissues. Men living in the Persian Gulf Littoral are exposed to a high atmospheric temperature varying between 125° F. and a minimum of 85° F. Hence the European has to sweat continuously to keep his skin temperature at such a level that the circulating blood can be sufficiently cooled. Under these conditions diuresis is so reduced that urine is passed perhaps only once a day.

The agent which is responsible for the phenomena of heat-stroke and heat-exhaustion is, of course, heat: in other words, it is the luminous and dark electro-magnetic waves, extending from a wave-length of 5,000 to 8,000 Angström units in the visible range, and below 8,000 A. to about 20,000 A. in the invisible or infra-red range. Bright and dark rays of heat emanate from the sun; infra-red from secondarily heated, moisture-laden air, or from sun-heated buildings or ground; even from molten-metal containers in a foundry, or from a boiler surface; from the walls of a deep mine, and from many different situations in connection with the complexity of modern industry.

Moist heat is the most important factor, while the air temperature, wind velocity, and relative humidity are all of importance (*see also* p. 14). In calm air the normal human body can support an air-temperature of 100° F., if the relative humidity is less than 90 per cent.; 120° F. if less than 40 per cent.; and 140° F. if less than 15 per cent. But death occurs at 128° F. with a wind velocity of 20 miles an hour, and at 117° F. with a wind velocity of 56 miles an hour; such conditions are known to prevail in desert storms, such as the "simoom." Rogers found that the mortality of patients with a temperature of 107° F. was 8.3 per cent., with a temperature of 107° to 109° F. was 29·2 per cent., and with a temperature of over 109° was 69·2 per cent.

It is a matter of common observation that illness due to exposure to heat in the absence of sunlight is common amongst workers in deep mines and stokers in the stokehold of steamships. On the other hand, the blue-violet rays in sunshine have a noxious effect on patients suffering from pellagra and smallpox and cause photophthalmia and some blindness. Moreover experiments that have recently been made with sunlight show that the ultra-violet rays of the sunshine are capable of a much deeper penetration into the tissues of man than has been generally supposed. A certain amount can be learned from the effects of high environmental temperatures upon animals occupying different levels in the biological scale. Thus frogs suffer from "heat-stroke" when the temperature of the water rises to 104° F.; it has been found that the lactic acid concentration in the blood and muscles of the amphibian rises to such a height that it becomes

completely paralysed. Guinea-pigs begin to succumb to heat-stroke when the shade temperature rises to 110° F., rabbits when it reaches 116° F., and man at 130° F. According to Halliburton, however, man succumbs if his body temperature be kept at 108° F. for one hour.

Hyperpyrexia due to heat is complicated in man by the effect of sweating upon the concentration of salts in the blood, so that even in a cool atmosphere, heavy manual labour, causing generous perspiration over long periods of time, when associated with deficient salt intake will, in experimental individuals, produce severe symptoms which can be cured by salt ingestion, as shown by Moss in 1927.

It thus appears possible that auto-intoxication, and not suppression of the sweat mechanism, is the primary factor in the production of heat-stroke.

The term "heat-stroke" conveys the suggestion that heat is the leading ætiological factor in the various morbid conditions which custom has grouped under this and similar names.

Heat-exhaustion may occur in any climate, high atmospheric temperature being the essential factor. *Heat-hyperpyrexia* has a peculiar endemicity; while *sun-traumatism* results exclusively from exposure to the direct rays of the sun.

The differences are summarized in the table on the opposite page.

HEAT-EXHAUSTION

Definition.—Sudden faintness, or fainting, brought about by exposure to high atmospheric temperature.

Ætiology.—The healthy human body can support with impunity very high atmospheric temperatures. In many parts of the world men live and work out of doors in temperatures of 100° or even of 120° F. The stokers of steamers, especially in the tropics, discharge for hours their arduous duties in a temperature often over 150° F.

When, however, the physiological activities have become impaired, by disease, especially by heart, kidney, liver or brain disease, or by malaria, by alcoholic or other excess, by fatigue, by living in overcrowded rooms; or when the body is oppressed by unsuitable clothing; or in the presence of a combination of some of these factors—then high atmospheric temperatures are badly supported, the innervation of the heart may fail, and syncope may ensue.

Symptoms.—When attacked with heat-exhaustion the patient feels giddy, and perhaps staggers and falls. He is pale; his pulse is small, soft, and perhaps fluttering; his breathing is shallow, perhaps sighing, never stertorous; his pupils are dilated; his skin is cold; his temperature is subnormal; and he may be partially, more rarely quite, unconscious. Usually, after a short time, he gradually recovers; very likely with a splitting headache and feelings of prostration. In a small proportion of cases the faint is not recovered from, and death ensues.

ALASTRIM.

Note patches on inner side of thigh, above knee, around septic cut.
(After L. M. Moody, "Ann. of Trop. Med. and Parasit.")

Photo Dr. A. D. B[illegible]

PELLAGRA RASH ON FEET.

Dorsa of feet had been exposed to sun in area between turned-up trousers and uppers of shoes.

PLATE XI

HEAT-STROKE

	Heat-Exhaustion (Syncope)	Heat-Hyperpyrexia (Auto-intoxication)	Sun-Traumatism (Sunstroke) (Mental irritability)
Onset.	Sudden faintness.	(*a*) *Prodromal* (not constant). Restlessness, vertigo, headache, mental confusion, anorexia, thirst, sighing, visual disturbances, nausea, vomiting, urinary irritability, suppression of sweat.	Gradual
	Symptoms : Giddiness fainting, shock.	(*b*) *Symptoms* : Rapid hyperpyrexia, coma, pulmonary congestion.	*Symptoms* : Cerebral irritation, light and sound intolerance, meningeal congestion, delirium, restlessness.
Cause.	Exposure to high temperature, especially in stokeholds.	Direct action of solar or atmospheric heat on body causing auto-intoxication.	Prolonged exposure to solar rays.
Signs.	*Conducted heat.*	*Conducted heat.*	*Radiated heat.*
Face.	Pallor.	Flushed.	
Pupils.	Dilated.	Contracted.	
Pulse.	Small, soft, fluttering.		Rapid, full.
Respiration.	Shallow, sighing.	Stertorous.	
Temperature.	Subnormal.	Hyperpyrexial.	Moderate.
Skin.	Cold and clammy.	Dry, sweat suppressed.	Dry.
Urine.		Small quantity ; may be suppression; offensive. Albumin, indican, R.B.C.'s present, casts.	Albumin.
Clinical.		Sphincter control may be lost.	
Reflexes.	Present.	Erratic.	Exaggerated.
Consciousness.	Partial or temporary loss.	Coma.	Partial loss. May be delirium.
Death.	Rare.	Common.	Unusual.
Treatment.	Stimulation ; Lay patient in cool place ; brandy ; ammonia to nostrils, etc., etc.	Rapid reduction of temperature ; cold bath, ice packs, continuous spray, ice enemata ; chloral or pot. bromide if restless. Stimulate only after sweating begins. Artificial respiration.	Quietude ; cool, airy, dark room ; ice cap on head ; empty bowel ; bromides.
Avoid.	Douching too freely.	Reduction below 104°F.	Alcohol.

Treatment.—In syncopal heat-stroke the patient should be laid at once on his back in a cool, airy, and shaded place. His clothes should be loosened, a little water dashed on his face and chest, and ammonia held to his nostrils. If necessary, a stimulant may be given by the mouth, or injected into the rectum or hypodermically. It is a mistake to douche these cases too freely. The object is rather to stimulate than to depress.

HEAT-HYPERPYREXIA

Synonyms.—Heat-stroke; Insolation; Thermic Fever; Siriasis.

Definition.—An acute condition developing in the presence of high atmospheric temperature, and characterized by sudden incidence of hyperpyrexia, coma, and extreme pulmonary congestion and œdema.

Geographical distribution.—Heat-hyperpyrexia appears to be remarkably restricted. Although this type of disease has been reported as occurring in many countries, on making careful investigation it will be found that a large proportion of the reputed cases are really examples of other diseases, more especially of cerebro-spinal fever, apoplexy, tuberculous meningitis, alcoholism, cerebral malaria, or some other phase of acute disease, but not of true heat-hyperpyrexia.

The endemic areas are—in America, the east coast littoral of the United States, more especially in the great towns, the Mississippi valley, the coast of the Gulf of Mexico, the valleys of the Amazon and of the La Plata, and the South Atlantic coast; in Africa, the valley of the Nile, the coasts of the Red Sea, and a low-lying part of Algeria near Biskra; in Asia, Syria, Iraq, the valleys of the Indus and Ganges, Lower Burma, Tonquin, and South-East China; in Australia, the Murray River district, the Queensland coast, and possibly the plains of Sydney. It is not met with on the high seas, although it is well known on ships in the narrow, land-locked Red Sea and the Iranian Gulf. During the Great War dangerous cases occurred most numerously in Iraq, especially during July, 1917, when for three days the temperature reached 122° F. in the shade, and 135° F. in the interior of double fly-tents.

Ætiology.—New-comers to the endemic areas and Europeans are more liable than natives or residents of long standing. Men over forty are more susceptible than those of younger age. Apparently, long residence confers a relative, although not an absolute immunity.

All ages and both sexes are susceptible; but in consequence of their habits and more frequent exposure to the predisposing and immediate causes, men are more liable than women.

Heat-hyperpyrexia has generally been attributed to direct action of atmospheric or solar heat on the body. Many theories of the *modus operandi* of this assumed cause have been advanced. Among these may be mentioned superheating of the blood by the high temperature of the surrounding atmosphere. Most authorities agree that a process of auto-intoxication occurs, as evidenced by the indicanuria, so that acetone and diacetic acid occur in the urine of 12 per cent. of cases. Hearne has pointed out that heat-hyperpyrexia is associated with

suppression of sweat, which may precede the onset of serious symptoms by 48 hours, for after prolonged exposure to high temperatures the sweat apparatus becomes exhausted and the glands cease to function. With sweating suppressed, the body-temperature tends to adjust itself to that of the atmosphere, but, in view of the increased respiratory and nitrogenous changes, is unable to do so. Coma, delirium, and convulsions appear directly the body-temperature reaches 108° F. Hypodermic injections of atropine have been shown to predispose to heat-hyperpyrexia through its action upon the sweat-glands; and somewhat similar results have been produced in lower animals by Cramer, by injection of β-tetra-hydronaphthylamine, which over-stimulates the thyroid-adrenal apparatus. The cramps are attributed to the coagulation of myosin in the affected muscles (Cajamian).

Blood chemistry.—Marked dehydration is associated with an increase in the percentage of hæmoglobin to 110 per cent., and a corresponding increase in the red blood-cells. The leucocyte count is also slightly increased. There is a diminution of the blood chlorides, and plasma bicarbonate, but a rise in lactic acid, blood-sugar and, usually, blood-urea (Marsh).

The earliest sign of impending hypochloræmia is low, or absent, urinary chlorides. A valuable rough test is to take 5 c.c. of the patient's urine in a test tube, and add 5 drops of concentrated nitric acid and a few drops of a 1-per-cent. solution of silver nitrate. Normally a thick white curdy precipitate forms, and a slight haze or no change indicates that chlorides are absent. Sugar and acetone are occasionally found, and also a trace of albumin and a few hyaline casts.

Pathology.—A notable feature of fatal hyperpyrexia is the early appearance of rigor mortis. The blood is remarkably fluid, or but feebly clotted. The venous system is loaded, dark fluid blood pouring from the phenomenally engorged lungs and other viscera on section. Both blood and muscles are said to yield an acid reaction more or less pronounced. It has been stated that the red blood-corpuscles are crenated and do not form rouleaux. If the post-mortem examination is made shortly after death and before decomposition changes have set in, the heart in early rigor mortis, particularly the left ventricle, will be found remarkably rigid; this is sometimes described as being of "woodeny hardness." There may be some venous congestion of the meninges, but the brain itself shows no important vascular or naked-eye changes. On microscopic examination, necrotic changes in the ganglion cells, with chromatolysis of the nuclei, are found. The cerebrospinal fluid is clear and under pressure. Cortical changes in the suprarenals have been described. The intestinal mucosa, as well as that of the stomach, is swollen, and exhibits patches of congestion. The temperature of the cadaver continues to rise after death, and may reach 114° F.

Symptoms.—Though sometimes coming on suddenly during exposure to the sun, heat-hyperpyrexia is very often preceded by a distinct prodromal stage. It frequently develops independently of any direct exposure to the sun; not seldom the attack comes on during the night.

Among prodromata, which may show themselves with greater or less distinctness for an hour or two or even for a day or two before the full development of the attack, are great disinclination for exertion, pains in the limbs, drowsiness, vertigo, headache, mental confusion, sighing, anorexia, thirst, intolerance of light—sometimes accompanied by chromatic aberrations of vision—suffused eyes, nausea and perhaps vomiting, præcordial anxiety, suppression of sweat, urinary irritability, sometimes a sense of impending calamity, an hysterical tendency to weep, and a quickened pulse. The irritability of the bladder is a valuable and easily recognized danger signal. Willcox has drawn attention to the loss of knee-jerks which occurs, and their return is a favourable indication.

The first indication of anything wrong may be a short stage of restlessness, or possibly of wild delirium. This brief preliminary stage rapidly culminates in coma, complete unconsciousness, and high fever, quickly passing into hyperpyrexia which may reach 110° F. The pupils, unless immediately before death when along with the other sphincters they relax, are contracted. The reflexes are partially or wholly in abeyance. There may also be, especially in the graver cases, free watery purging, the dejecta as well as the skin of the patient emitting a peculiar and distinctive mousy odour. The scanty urine may contain blood-corpuscles, albumin, and casts.

Willcox distinguishes different clinical types of heat-hyperpyrexia :

(1) *Gastric type.*—A most deceptive form, in which the axillary temperature is normal, the rectal temperature raised, and gastric symptoms predominate, with congestion of the liver. A fatal hyperpyrexia may develop without previous warning.

(2) *Choleraic type.*—This form is of sudden onset, with purging and general resemblance to true cholera ; it may be fatal within three or four days. The rectal temperature may rise to 110° F. after death.

(3) The *true heat-hyperpyrexia*, in which nervous symptoms predominate, has already been described. It accounts for 70 per cent. of the cases. The temperature may rise to 113° F. for a short time, and the patient yet recover (Marshall).

Unless active measures to lower temperature are taken early in the progress of the case, and vigorously carried out, in the great majority of instances death will occur within a few hours, or even minutes, of the onset of insensibility. The immediate cause of death is generally the failure of respiration. Rarely do cases linger for a day or two. Partial recovery is sometimes followed by relapse. In favourable cases the disease usually terminates by crisis. Convalescence is rapid. Unless the patient is moved into different surroundings a relapse may occur ; two or even three have been recorded. Occasionally cerebral or cerebellar symptoms may persist.

Usually heat-hyperpyrexia is much more dangerous than ordinary heat-exhaustion, but the death-rate may be materially reduced by early and judicious treatment. In Iraq during the Great War, the

case-mortality among British troops from this cause was about 8 per cent.

Diagnosis.—The presence of high fever is sufficient to differentiate heat-hyperpyrexia from sudden insensibility caused by uræmia, by diabetic coma, by alcoholic and opium poisoning, and by all similar toxic conditions. Carbon monoxide and hydrogen sulphide poisoning must also be thought of. Cerebral hæmorrhage, particularly pontine, may, after some hours, be followed by high temperature ; but here the febrile condition follows the insensibility, whereas in heat-stroke the febrile condition precedes insensibility. The diagnosis from a cerebral malarial attack may be very difficult ; chief reliance has to be placed on the history, if obtainable, on the condition of the spleen, and especially on the result of microscopic examination of the blood ; but sometimes the parasites, usually subtertian, may not be demonstrable for two or even four days from the onset. Malarial fevers and the early stages of the eruptive fevers in children are very apt to be regarded as heat-stroke, particularly if there has been recent exposure to a hot sun. Cerebro-spinal fever, so often mistaken for heat-hyperpyrexia, may be recognized by the occipital retraction, the irregular pupils, the frequent occurrence of strabismus, Kernig's sign, the comparatively low and fluctuating temperature, the associated herpes, the initial rigor, and its duration. Uncomplicated heat-stroke is accompanied by hypochloræmia, dehydration, absence of urinary chlorides, excess of lactic acid, and low content of bicarbonates in the blood.

Marsh states that during a heat-wave in the Iranian Gulf mild cases of heat-exhaustion are usually in the majority, and so it is difficult, sometimes, to distinguish cases of pure fright from genuine cases. Real cramps constitute a valuable diagnostic sign. They are so extremely painful that the patient cannot sustain a conversation and the affected muscles can be felt forcibly to contract.

Treatment.—In all fulminating fevers, including heat-hyperpyrexia, occurring in warm climates, if malaria be suspected, particularly if the parasite be discovered in the blood, quinine should be injected intravenously or intramuscularly at once (7–10 gr. of the dihydrochloride), or given by enema as directed for malaria ; this dose should be repeated three or four times at intervals of four hours. Should there be any suspicion of opium or alcohol poisoning, the stomach should be washed out. In every case of heat-stroke, whether it has been deemed advisable to administer quinine or not, attempts must at once be made to reduce temperature by such rapidly acting measures as the cold bath, or ice applied in various ways to the head and body. Antipyretic drugs are of very little service, even if, in consequence of their depressing action on the heart, they be not actually dangerous ; in all serious cases of heat-stroke such drugs must be carefully avoided. The patient should be placed on a wet sheet supported upon bed cradles, thus forming a moist chamber in which he lies ; the whole may rest upon a rush-covered bed or " angareeb."

Mackintosh sheets must be avoided. The continuous water-spray with iced water, together with an electric fan, simulates the natural process of sweating to the best advantage. Ice-water enemata are also recommended; to these, should convulsions and restlessness supervene, potassium bromide or chloral may be added. Rubbing the skin with ice, by constricting the capillaries, apparently only obstructs evaporation. A thermometer should be kept in the rectum and the application of cold should be discontinued so soon as the thermometer in the rectum has sunk to 104° F., or, in cases of simple thermic fever in which the temperature has not exceeded 106° F., when it has fallen to 102° F. If powerful antipyretic measures are carried beyond this point the fall of temperature may continue below the normal, even to as low as 91° F., and dangerous collapse ensue. In the absence of electric fans an iced wet sheet may be wafted up and down over the patient's abdomen by means of a punkah-like arrangement.

On discontinuance of the iced sheet, the patient should be wrapped in a dry blanket; very likely, perspiration, a favourable sign, will then set in. Stimulants may now be necessary. Strychnine, owing to the marked tendency to convulsions incidental to heat-stroke, must on no account be used as a cardiac stimulant; Chandler, as the result of his large experience, recommended the injection of 40 min. of tincture of digitalis. Convulsions are best controlled by cautious venesection. As death in heat-stroke generally results from failure of respiration, Hearne and others strongly recommend artificial respiration when the breathing threatens to become suspended; it should be maintained for half an hour or longer. Lumbar puncture is indicated in cerebral cases as a rational method of relieving intracranial pressure. Intravenous or subcutaneous injections of normal saline are indicated in the choleraic forms. Gastric cases should receive a liberal supply of bicarbonate of soda—30 gr. every two hours.

During convalescence great care must be exercised to shield the patient from all influences calculated to provoke relapse. The power of sweating may be in abeyance for three weeks or longer.

Prophylaxis.—Patients in hospital are especially liable to develop heat-hyperpyrexia. The most valuable practical method i. to attempt to forestall the advent of heat-stroke by periodically inspecting the patients to find out those with commencing suppression of sweat, urinary irritability, restlessness and insomnia.

A heat-stroke hut, or treatment room, or even a heat-stroke ward, is a most desirable addition to hospital equipment in the tropics. This has led to the construction of special refrigeration apparatus.

A refrigerating apparatus consists of a horizontally placed ammonia compressor working in conjunction with a brine-circulating system. At Masjid-i-Suleiman in South Persia (Anglo-Iranian Oil Fields) heat-stroke cases, and indeed all cases of fever, are, in outlying stations during the heat of the day until the cool hours between midnight and five a.m., kept in a cold-storage chamber, attached to the ice-plant. During

the coolest part of the night they are put into a fast ambulance and taken to the nearest heat-stroke hut where they are kept until complete recovery has taken place.

As the result of these measures the incidence of heat-stroke has been greatly reduced and has almost ceased to count as a cause of invalidism. The cost, according to Rennie, of maintaining such a cool chamber, is £400–£500 per annum.

Efficient methods of cooling the air are employed in industry in many parts of the world. These include methyl chloride or ammonia refrigerating machines, or the use of the cooling powers of evaporating water at atmospheric temperatures and in *vacuo*. Air-conditioning of houses and dwelling-rooms is commonly found in New York and other American cities, and the matter is solely one of expense (*see* p. 24).

Acclimatization.—Some organizations in the tropics endeavour to avoid the ill-effects of heat by ensuring fitness and acclimatization of the workers. In the Witwatersrand gold mines, candidates for employment are subjected to a test in rooms artificially heated to 94° F., wet-bulb, and are then graded on their reactions, suitable candidates being put through a further course involving exposure to high temperatures in stages and lasting, sometimes, for fourteen days.

Fewer casualties occur from heat among men born and bred in the hot climates than among those reared in temperate climates. While there is a general agreement that excessive alcohol consumption is contra-indicated, less attention has been paid to the profound effects that may arise from shortage of water. It has been shown that up to three gallons of drinking water a day are necessary for a man at work in the summer time in the Deccan. The "poisonous" property of water is neutralized by the addition of half an ounce of salt to the gallon of water. There is no evidence that alcohol in moderation is harmful. Constipation in the hot season is almost physiological and must be avoided. (*See also* pp. 14 *et seq.*)

SUN-TRAUMATISM

In cases of this type, after prolonged exposure to the sun, a febrile condition is established. It is sometimes of great severity, being characterized by intense headache, a rapid full pulse, a pungent dry skin, intolerance of light, sound, and movement, and occasionally by vomiting or delirium, suggesting meningeal congestion. The acute phase may be quickly recovered from, or may prove very persistent and last for days or weeks. It may leave no injurious effects, or may be followed by a variety of transient or more permanent morbid nervous phenomena.

Ætiology.—Manifestly, the symptoms produced are not due to heat, for such effects do not result from exposure to the heat of a furnace, however intense. There appears to be some special element in the solar rays capable of injuriously affecting the tissues, particularly

if they have not become gradually habituated to sun-exposure. In this connection we are forcibly reminded of the phenomena of the actinic rays of the solar spectrum, and of the remarkable tissue changes induced by the Röntgen rays.

Treatment.—Patients suffering from sun-traumatism must be kept as quiet as possible in a cool, airy, and darkened room. The head should be kept shaved, and cold applied to the scalp. The bowels must be free; food should be light and unstimulating, and alcohol in every form strictly forbidden. Restlessness and insomnia are best treated by the bromides. For a considerable time the patient will be troubled with loss of memory, and feebleness of intellectual power and of the faculty of concentration. He may be irritable, liable to headache, and extremely sensitive to heat—more particularly the heat and glare of the sun. So soon as he is able to be removed he must be sent to a cooler climate, and there remain until all trace of his illness has completely disappeared. Indeed, it is questionable if the subject of pronounced sun-traumatism should ever again risk the dangers of a tropical climate; certain it is that he should not return to the tropics so long as the slightest evidence of cerebral trouble remains.

Section II.—VITAMIN DEFICIENCY DISEASES (AVITAMINOSES).[1]

Preliminary Statement

The term "avitaminosis" (or devitaminosis) is applied to a series of apparently dissimilar clinical states of which the main ætiological factor is concerned with the constitution of the dietary. It is generally understood that it is not the quantity of the diet, but its quality, or the unbalance of its ingredients, which can bring about such serious chemical changes in the human body. The process is to be regarded as being quite distinct from actual starvation, in which state none of these peculiar phenomena need necessarily occur. Dietary deficiencies, then, are the gradual withdrawal from the body of ingredients which are essential for the carrying out of certain elaborate biochemical processes and are therefore essential also for the maintenance of life. As will be seen in the sequel, the term "vitamin" was first applied to a substance which could be extracted from the outer layers of the rice-grain, and which was found to be essential for the maintenance of health of rice-eating peoples. Similar substances have been found widely distributed among foodstuffs, and several of them have now been isolated in a pure state. The exact chemical constitution of some of the vitamins has only recently been determined—they are evidently very highly complex bodies, and though small in quantity, their influence upon metabolism is determinative. They are regarded rather as stimulants, or catalysts, than as entering into the structure of the tissues and are therefore termed by some "accessory food factors." At least ten of these substances are now known, and there are probably many more. Consequently deprivation produces the most diverse lesions (*see* Chap. II, p. 29).

CLASSIFICATION OF THE VITAMINS

Vitamin A_1.	Antixerophthalmic, or anti-infective factor.
Vitamin A_2.	Closely related physiologically to A_1.
Vitamin B_1.	Antineuritic, beriberi-preventive factor.
Vitamin B_2.	"Riboflavin." Connected with oxidizing mechanism in the tissues.
Vitamin B_3, B_4, B_5.	Growth factors detected in certain animal experiments, but relation to human nutrition not yet clearly defined.
Vitamin B_6.	Rat anti-dermatitis factor.
	PP factor, nicotinic acid, or nicotinamide ; antipellagra factor.

[1] The subject is developing at such a rate that it is impossible to present more than a mere outline of the generally accepted facts.

Vitamin C. Ascorbic acid. Anti-scorbutic factor.
Vitamin D_2. Calciferol. Antirachitic factor; the artificial product of the ultra-violet irradiation of ergosterol.
Vitamin D_3. Natural product, isolated from high-potency liver-oils known to contain several antirachitic factors.
Vitamin E. Antisterility factor.
Vitamin K. Anti-hæmorrhagic vitamin concerned with blood-clotting.

The fat-soluble vitamins are A, A_2, D_2, D_3, E and K.
The water-soluble vitamins are B_1, B_2, B_3, B_4, B_5, B_6 (PP), C.

Vitamin A.—This substance is found in animal tissues, especially the liver, and arises from the breakdown of a plant pigment, β carotene, which is therefore usually referred to as *provitamin A*. In fact, four compounds act as provitamin A, namely, α, β, and γ carotene and kryptoxanthin, all containing a β-ionine ring, which must be present in any substance convertible in the body to vitamin A. β carotene, however, has two such rings and this explains why it preserves greater biological activity than the other provitamins.

Carotene is a hydrocarbon, $C_{40}H_{56}$, and is found in all green plant tissues and in certain roots and fruits, e.g., carrots and palm fruits. Green vegetables and carrots have no vitamin A, but have carotene.

In the animal body, probably in the liver, it is broken down by water. $C_{40}H_{56} + 2H_2O = 2C_{20}H_{30}O$. This alcohol is a pale yellow, viscous oil, and is known as vitamin A_1.

A_2 closely resembles vitamin A in chemical characters, and was discovered in the liver oils of freshwater fishes. It probably has a biological activity similar to that of vitamin A_1.

Vitamin A is probably the physiologically active agent, but carotene and the vitamin produce the same effect. A chemical blue colour is formed by this vitamin with antimony trichloride. The international standard unit is 1 γ (0·001 mg.) and 3 to 5 γ are found sufficient to protect young rats.

An adequate supply of vitamin A in the diet is essential for satisfactory growth in childhood and for maintenance of a normal resistance against infection in youth and in adult life. The characteristic changes in the tissues of individuals deprived of vitamin A show themselves in keratinization of epithelial structures. (In experimental rats deficiency of vitamin A causes shrinkage and dysfunction of the salivary glands and atrophy of the intestinal villi, and permits bacteria to enter the glands.) In cases of prolonged deficiency the cutaneous epithelium may become so keratinized as to produce a dry atrophic condition known as "toad skin" or phrynoderma, which is found in East Africa, Ceylon and China (Frazier and Au), and is comparatively rare in western Europe. Some have suggested that the frequency of renal calculi in India and China is also due to vitamin-A deficiency.

Lathyrism is a disease associated with degenerative changes in the spinal cord similar to those occurring in dogs fed on a vitamin-A deficient diet, and it is suggested that the absence of vitamin A and carotene from the diet allows a neurotoxin in the peas to exert a harmful influence on the central nervous system.

Vitamin-A deficiency undoubtedly plays a leading part in the causation of xerophthalmia, when the cornea becomes opalescent, and superficial ulcers appear in the degenerate epithelium till the patient becomes blind. Wright, in Madras, believed it was the chief cause of blindness in children in India, and Nicholls came to the conclusion that in Ceylon more than 65 per cent. of blindness in children is due to this cause.

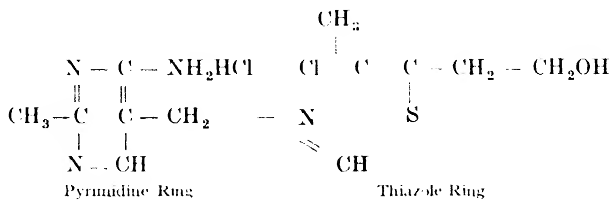
Bitot's spots, yellowish, irregular, foamy patches on the conjunctiva, which are seen in the poorer class of children in Southern India and East Africa are attributed to a similar deficiency.

It is coming to be recognized, also, that a mild form of night-blindness (hemeralopia) is due to vitamin-A deficiency. This vitamin plays a direct rôle in the process of bleaching and regeneration of the visual purple in the retina. So well-marked is this dark adaptation that it is now being largely used as a method for detection of vitamin-A deficiency in a population. The detection of deficiency (Mutch and Griffiths, 1937) is known as *visual dysadaptation.* The test measures the power of distinction, under different illumination, of a series of cards, viewed through a series of Tscherning photometric glasses. The eyes are tested under optimal dark adaptation, i.e., after fifteen minutes.

It is claimed that large doses of vitamin A produce improvements in hyperthyroidism, and an antagonism between it and thyrotoxin has been demonstrated. The vitamin-A content of food is not affected by ordinary processes of canning or by such exposure to heat and air as occurs in ordinary cooking. In butter it is resistant to heat to 120° C., but it is readily destroyed by aëration.

It is important to remember that there are seasonal variations in the vitamin-A value of dairy produce. Generally speaking, the vitamin-A value of milk, butter and eggs tends to be at its lowest in the early part of the year, and at its highest in the months of June and July.

Vitamin B_1 (*Aneurin;* American, *Thiamin;* sometimes also known as vitamin F).—This is the well-known anti-beriberi or antineuritic vitamin (*see* p. 440). The isolation of the crystalline vitamin was effected by Jansen and Donath from rice polishings. The formula is $C_{12}H_{18}ON_4Cl_2S$ and its constitution for vitamin B_1 hydrochloride:—



It has finally been synthesized by Williams and Cline, and it is now possible to produce it in large amounts. The physiological activities of the synthetic product is identical with natural B_1.

Deficiency or absence of this vitamin leads to malnutrition of the nervous system, and also to disorders of digestion, dysfunction of the endocrine glands, and increased susceptibility to infection. It is contained in the cuticle, or pericarp, of grain, and in the aleurone layer of rice (Fig. 49), but the richest supply is the germ, or embryo, of wheat, rice, barley, and rye. An especially rich source of the vitamin is the Chinese bean, "kachang hijau" (*Phaseolus radiatus*). Eggs and tomatoes also yield a rich supply, but fresh meat is deficient, and so is butter, fat, fish, canned meats and cheese. Yeast, from which is made the commercial *Marmite,* a substance containing also the PP factor, is also a rich source of supply.

The natural product is less affected by exposure to oxygen than are the other vitamins, and is not specially affected by heat (in the canning process,

it will stand autoclaving at 120° for thirty minutes). From the extract of the natural products the active principle can be separated by absorption on solids such as fuller's earth, and such activated earths have been used as a method of administering vitamin B_1 by the mouth. For intravenous or subcutaneous injection, the hydrochloride of the vitamin is employed.

It has recently been realized that aneurin plays a part in one phase of carbohydrate metabolism. In the form of a compound with pyrophosphoric acid it acts as the co-enzyme to the enzyme which breaks down pyruvic acid, which is one of the intermediate products between glucose and carbon dioxide. A deficiency in vitamin B_1 causes a lowering of the pyruvate-metabolizing mechanism with the result that the amount of pyruvate in the blood tends to rise. This abnormality can be detected, either by estimating the amount of pyruvic acid by direct combination with 2 : 4-dinitrophenyl-hydrazine or, less accurately, by determining the amount of substance in the blood which will combine with the bisulphites. Hence the importance of BBS (bisulphite binding substance). Pyruvic acid is not *toxic* in itself, but is indicative of dysfunction of the body cells, and is derived from lactic acid.

Vitamin B_1 plays a definite part in metabolism, and it is claimed by Cowgill that the minimum requirements of man can be ascertained from the body-weight and the calorific value of the diet, thus:

Vitamin intake (in international units) = Calorific intake × wt. (kg.) × 0·0284 (The international unit is 0·001 mg. or γ).

Peters has shown that convulsions in beriberic animals are due to excess of lactic acid in the brain; owing to deficient oxygen absorption, and this is the basis of the "bradycardia" test in rats, which is taken as a gauge of B deficiency (excess of lactic acid in the cardiac muscle).

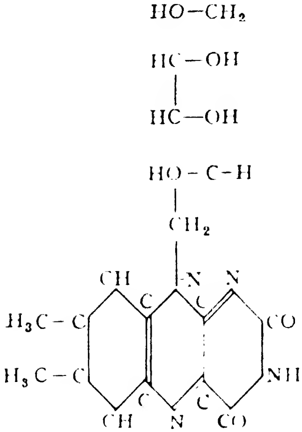
The minimum requirements of an adult taking a daily diet of 3,500 calories can be taken at 550 international units. The "beriberi danger-line" appears to be about 200 units.

There is a danger of vitamin-B_1 deficiency when patients are on a restricted diet for gastric or duodenal ulceration, and it has been shown that the poly-neuritis of chronic alcoholism is traceable to a shortage of this vitamin. The main initial features of a vitamin-B_1 deficiency are loss of appetite and loss of weight. When the latter has fallen to 65 per cent. of possible maximum, the terminal symptoms appear, such as decreased sugar tolerance, nervous symptoms, changes in temperature, faulty vision, bradycardia, and, sometimes, œdema. In children it is advisable to err on the excess side of this vitamin, for it is certain that a large excess can be present wi hout causing any ill effects. In pregnancy daily doses as high as 1,000 units are requisite.

Vitamin B_2 (*Riboflavin*).—Formerly it was thought that one water-soluble vitamin was concerned in the genesis of pellagra and allied conditions of laboratory animals, but later work demonstrated that at least *two* substances were concerned. One of these is still known by the original name vitamin B_2 or, better still, riboflavin (formerly lactoflavin), the other as vitamin B_6 (or ?, PP factor). Vitamin B_2 is a yellow fluorescent pigment which is found in liver, eggs, and milk,[1] and it is responsible to a large extent for the greenish-yellow colour of whey. When freshly isolated it is a golden-brown crystalline solid of the composition $C_{17}H_{20}N_4O_6$ (6-7 dimethyl-9-ribityl-isoalloxazin). It has been synthesized by Kuhn and his colleagues. As at present

[1] It is hardly necessary to state that the product from eggs has been called *ovoflavin*, from milk *lactoflavin*, and from liver *hepatoflavin*.

understood the vitamin B_2 complex can be represented by the following formula :



Riboflavin portion of B_2 complex

Nicotinic acid : Pyridine B carboxylic acid

Previous to 1934 35 vitamin B_2 was considered to be a definite entity which differed from B_1 in being heat-stable and in various other respects, notably its action on experimental animals. In 1934 György showed that lactoflavin was the main rat-growth factor. Later Harris, Chick, Birch and Elvehjem showed that it would not affect pellagra in rats, chickens, dogs, or man, and in 1936 opinion was that the curative agents for human pellagra, canine blacktongue and chicken pellagra still remained to be discovered. It was also found that the flavins from all sources (lactoflavin and hepatoflavin) were chemically and physiologically identical.

This work synchronized with that of Knight in England and Mueller in America upon the identity of a specific substance in fresh-meat infusions which rendered it essential for the growth of delicate pathogenic bacteria. The former worked upon staphylococcus ; the latter mainly upon diphtheria. Finally, nicotinic acid and nicotinamide were found to constitute the missing link.

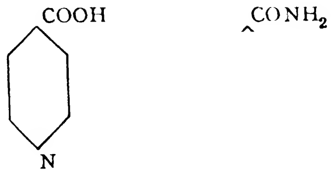
Probably riboflavin is found universally in nature, and is an enzyme concerned with oxidation in the body tissues. In bringing about metabolic changes in the organism it acts in combination with phosphoric acid. Riboflavin is indispensable to the normal functioning of the oxidizing system of cells. All else that is known at present is that it cannot be synthesized by the organism and that it is essential to cellular respiration. There are indications that a deficiency of it may be associated with one form of cataract.

Vitamin B_6 and the *PP factor*.—For some fifteen years it has been suspected that pellagra in man and allied conditions in rats and dogs were deficiency diseases. Provisionally the factor involved was given the label PP, indicating pellagra-preventive factor. (In the U.S.A. it has been known as vitamin G.)

Nicotinic acid is a simple carboxylic acid of pyridine which is prepared by the oxidation of nicotine : it and its amide—nicotinamide—have now been shown to replace some essential substance which is found in meat infusions and which is necessary for the growth of certain pathogenic bacteria.

Both these substances exert an action on animals which is identical with that of that portion of vitamin B_2 complex, known as the pellagra-preventive PP factor, and also as the blacktongue (of dogs)-preventing vitamin.

The work of Elvehjem and his colleagues at Madison, Wisconsin, has clearly proved that pellagra-like conditions in certain animals can be cured by nicotinic acid or its amide, the relationship of which to each other (*see* p. 462) can be expressed as:



The application of these substances to the treatment of human pellagra has proved a success, and cases respond with remarkable promptitude to the administration of amounts ranging from 100–500 mgm. by the mouth, or to repeated dosage by the injection of quantities to 10–20 mgm.

The exact functions of nicotinic acid in the body are as yet unknown, but the amide is part of the molecule of the co-enzyme (co-zymase) which plays a part in carbohydrate breakdown. There is at present no international standard for nicotinic acid, nor any estimations of the amount present in common foodstuffs. The richest sources are liver, kidneys, milk, eggs, and cheese. The amounts of nicotinic acid are readily ascertainable by chemical analysis. A colour test has been described for the detection of nicotinic acid in the urine. Spies and his colleagues find that the test is negative for pellagrins, but positive with normal urines.

The rat anti-dermatitis factor (*vitamin* B_6) is now considered to be different from the PP factor. It is essential for the normal growth of the rat, and is destroyed by ultra-violet radiation. This vitamin is present in yeast and in the muscle of salmon, herring, and haddock. Mammalian liver is a good source, but fish liver is very deficient in it, and egg-white quite devoid of it. The pellagra-like disease of rats is entirely caused by deprivation of B_6.

The present knowledge of the vitamin B_2 complex is as follows:

(1) *Flavin*, which is a growth factor for rats, but which has no known effect on humans.

(2) *Nicotinic acid*, which will prevent and cure human pellagra, canine blacktongue, and rat nutritional panmyelophthisis (a general degeneration of the bone-marrow with anæmia).

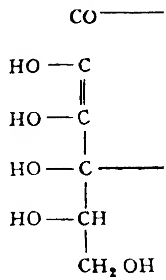
(3) *A rat-pellagra factor* (B_6).

(4) *A chicken-pellagra factor* with unknown human action.

Vitamin C[1] (*ascorbic acid, cevitamic acid*).—The pure vitamin—ascorbic acid ($C_6H_8O_6$)—was isolated from fruit juice by Szent-Györgyi in Hungary and independently by King and Waugh in America. It is a feebly acid substance closely related to the sugars, and has now been synthetically prepared. The international unit is 0·05 mg. of pure acid.

[1] This substance has been known for a number of years as "hexuronic acid," which was isolated by Györgyi from adrenal glands, oranges, and cabbage.

The formula for synthetic ascorbic acid is given as follows:



Many animals are capable of synthesizing ascorbic acid in their bodies; the cow may be cited as an example, for without any change in the diet, a sudden increase of vitamin C in the milk occurs in March.

An adequate supply of this vitamin is essential for the development of sound teeth, and there is an indication for the intake of vitamin C in febrile conditions, as depletion then occurs more rapidly.

An important point is that humans, especially children, show an increased fragility of the capillaries in spring-time, this being common in northern climates, where fruit and vegetables are scarce in winter. This, of course, is an early stage in the development of scurvy. To prevent the appearance of symptoms associated with the pre-scorbutic condition, children should be given at least 50 mgm. (1,000 international units) daily. Adults also require at least that amount, and in pregnancy the demand is greater, doses as large as 150 mgm. being indicated.

Scurvy has been recognized as a food-deficiency disease ever since the days of Lind in 1747, for it was his classical treatment of scurvy, as it occurred amongst the stricken seamen of the British Navy, by the juices of fresh oranges and lemons, that is so well known. The use of lime juice (probably lemon juice) has been recognized as a preventive against scurvy ever since his day. Holst and Frölich (1907) showed that scurvy could be induced in guinea-pigs by removing the greenstuff from the ordinary diet and by giving a diet composed of grain and water only. Later Fürst, whose results were later confirmed by Chick and Hume, found that scurvy could be prevented by peas and beans which had been soaked in water and allowed to germinate for two to three days; but even important observations appear to have been anticipated by Curtis, a surgeon in the English Fleet, as long ago as 1782.

In animals dying of scurvy the principal lesions show a close analogy with those characteristic of the human disease. Hæmorrhages occur in any position, but most frequently in the joints. The histological changes produced at the rib junctions in the guinea-pig are very striking, and they become progressively more extensive as the period of that deficiency increases. The most noticeable departures from the normal are a variable amount of irregularity of the junction as a whole, together with disarrangement and shortening of the rows of cartilage cells and of the trabeculæ, with an increased amount of blood in the marrow-cavity and a decrease in the thickness of the bone, especially near the junction. A very early symptom of lack of vitamin C is the change in the structure of the teeth. The growth of the incisors ceases entirely after fifteen to twenty days.

To protect a young guinea-pig from the ordinary symptoms of scurvy, a daily dose of 1·5 c.c. of orange juice is needed, while 3 c.c. are required to prevent degeneration of the dental pulp. On this basis it is estimated that a man requires 1,000 c.c. of milk, 200 grm. of boiled new potatoes or 60 c.c. of tomato juice daily. Although vitamin C is present in muscle and tissue, it is not stored in the animal body to the same extent as is vitamin A. Lemon juice forms the best source for concentration of vitamin C and the greater part of it is precipitated by basic lead acetate. Heating and fractional distillation destroy this vitamin, but decitrated lemon juice can be preserved aërobically at pH 1·0–0·6 for a week without loss of potency. Recent investigations have succeeded in isolating vitamin C as a pure chemical compound (ascorbic acid), and cases of scurvy in children have been cured by the action of this chemical substance. In 1924 Zilva discovered that active concentrates of this vitamin had a strong affinity for oxygen, and later Szent-Györgyi found that the properties of a substance he had isolated from the suprarenal cortex—hexuronic acid—were similar to those of vitamin C, and later still Tillmans showed that they were identical. Zilva has now shown that Bramley's Seedling apples keep their vitamin-C activity best when stored at $-20°$ C., and it has been shown by other workers that the vitamin C varies inversely as the nitrogen. The anterior lobe of the pituitary gland is especially rich in vitamin C, as is the suprarenal cortex. Reichstein and his collaborators have succeeded in synthesizing a product from l-*xylosone*, which is identical with ascorbic acid.

The reduction of the coloured dyestuff 2 : 6-dichloro-phenol-indophenol to a colourless substance by ascorbic acid is used as a test for determining vitamin-C deficiency. Vitamin C, like other water-soluble vitamins, is excreted in the urine, this being the cause of its depletion in the body, so that titration with a standard solution of the indicator gives a fairly accurate method of determining the amount of ascorbic acid excreted in twenty-four hours. The reaction must be carried out at an acidity represented by pH2 or 3, to reduce interference by other reducing substances. When an adult is receiving ample vitamin C in his diet, the daily excretion in the urine is 20–30 mg. ; when less than 15 mg. is excreted it is an indication of insufficiency.

To determine whether or not a patient is depleted of vitamin C, an intradermal test is carried out, depending on the time taken for a small quantity of a solution of dichloro-phenol-indophenol injected under the skin to lose its colour. The "capillary resistance" test is fairly reliable in infants and young children ; it involves counting the number of petechiæ formed in an area of skin of the forearm after raising the pressure in the limb a definite amount by means of a tourniquet.

Vitamin D (*antirachitic factor, or calciferol*).—This, the antirachitic vitamin, is contained in certain fats, notably in cod-liver oil, and is closely associated with vitamin A, but vitamin D is much more stable. It is 400,000 times as active as cod-liver oil. This vitamin is essential for the proper calcification of bones and for the formation of enamel on developing teeth ; it actually controls the deposition of calcium and phosphorus in the tissues, and it has been shown that it is particularly concerned with absorption of the phosphates. Steenbock and others showed that, in the absence of fat-soluble vitamins in the diet, irradiation of animals with ultra-violet light for ten minutes daily increases both the calcium and phosphorus in the blood, so that now blood-phosphorus estimations car be used to control the treatment of rickets. A definite diagnosis of rickets can now be made by radiography

long before any clinical symptoms become apparent. Later it was found that various fats and oils, both of animal and vegetable origin, can be activated by exposure to sunlight, so that the activated food has the same qualitative effect as cod-liver oil, and it has been found that the livers of rats which have not been irradiated are inactive.

Rosenheim and Webster, working with ergosterol, a highly unsaturated sterol obtained from plants, and notably certain yeasts after irradiation with ultra-violet light, demonstrated that this substance definitely cures rickets.

Irradiated ergosterol contains vitamin D in large amounts, and this has now been isolated in practically a pure crystalline form (calciferol). In this instance then the *provitamin* is converted into vitamin D by irradiation, and thus it becomes apparent that ultra-violet radiant energy is essential for the production of vitamin D, which lends truth to the well-observed fact that sunshine is essential for the prevention and cure of rickets. The amount of precursor substance (*provitamin D*) necessary to protect a rat against rickets is 0·0001 mg. or less. Calciferol (3 : 5 dinitro-benzoate) is remarkably stable, but on heating to 180° F. *in vacuo* it loses its antirachitic potency.

The stimulating effect of ultra-violet rays on calcification was first discovered in the case of children, but only at a later stage were observations confirmed by investigations made on animals.

Hess and Unger (1922) showed that the curative waves were confined to that part of the spectrum having wave-lengths of 300 μ or shorter. It is probable that vitamin D is produced in the skin itself or in the blood circulating immediately beneath the surface by the action of sunlight. Possibly, too, the consumption of large quantities of cereals may determine the onset of rickets.

Infantile tetany and rickets are closely associated, and this suggests that the lowering of the blood-calcium content in the former is connected with a deficiency of vitamin D. In its mode of action vitamin D probably promotes absorption of calcium and phosphorus from the bowel.

It is a well-established fact that the physiological demands for calcium by women during the later months of pregnancy is high, and is not met by the amount of calcium ingested in the ordinary diet. A deficient supply of vitamin D to the mother during pregnancy or lactation predisposes to rickets in the child.

The relation of vitamin D to the parathyroid gland.—The dramatic effects on bone and blood condition in osteitis fibrosa cystica of the removal of parathyroid cysts, or the effect of Collips' extract (parathormone) in tetany, must be ascribed to this relationship. Taylor, Weld, Branion, and Kay have presented evidence to show that action of large doses of irradiated ergosterol in producing a rise in serum calcium takes place through the intermediary of the parathyroid glands.

The definition of a unit of vitamin D is taken as 1 mgm. of the international standard solution of irradiated ergosterol. The biological estimation is judged by the "line test." Pure calciferol has an antirachitic activity of 40,000 international units per mgm.

Vitamin E (*Antisterility factor; α, β and γ tocopherols*).—There are now believed to be two or three closely related factors in this vitamin which play an important part in reproduction, apparently through the intermediation of the anterior lobe of the pituitary gland. Female animals, when deprived of a sufficiency of these essential factors, show a characteristic type of

secondary deficiency. In the male, a deficiency causes degeneration of the spermatogenic tissues. These vitamins are found in green plant tissues, but the richest source appears to be in the oil extracted from the wheat embryo, and these products have been employed with success in habitual abortion in women.

They are colourless and viscous oils, or alcohols, having the composition $C_{29}H_{50}O_2$.

Vitamin K was discovered by Dam in studying the nutrition of chicks. During the course of the observations they developed subcutaneous and intramuscular hæmorrhages, which did not respond to ascorbic acid, but did yield to extracts prepared from green vegetables and liver.

This vitamin is fat-soluble, and appears to play an essential rôle in the formation of *prothrombin*, because a deficiency in animals is associated with a greatly decreased clotting time of the blood, and it probably plays a part in thrombocytopenic purpura and other blood diseases.

CHAPTER XXIV

BERIBERI

Synonyms.—Kakke; Barbiers; Polyneuritis Endemica.

Definition.—Beriberi is a form of multiple peripheral neuritis occurring endemically, or as an epidemic, in most tropical and subtropical climates, and also, under certain conditions, in more temperate latitudes. The mortality is considerable, death usually depending on heart paresis.

History.—Beriberi was originally described by the early Chinese physicians, and is said to be referred to in the Neiching, a medical work attributed to Hwangti (B.C. 2697). The special nature of beriberi was recognized by the Dutch in the early years of their intercourse with the East. Later, it was studied by British physicians in India, particularly by Malcomsen, Carter, Waring, and Morehead. It was not until an epidemic in Brazil that beriberi began to receive attention from a later generation of medical men; and only when Anderson, Simmons, Scheube and Baelz took up the subject in Japan was it studied by modern methods, accurately defined, and its true pathology apprehended. Scheube and Baelz were the first to show distinctly that beriberi is of the nature of a peripheral neuritis simulating that of diphtheria and of alcohol—a view subsequently confirmed and adopted by Pekelharing and Winkler, and by most subsequent observers. Mainly owing to the investigations of Eijkman, Braddon, Cooper, Fraser, Stanton, Funk, Vedder, Hopkins, Hausette, Chick, and Margaret Hume, its principal it may not be the only—ætiological factor has been shown to be a dietary of which the staple ingredient is overmilled rice or other cereal which has been deprived of a substance, one of the vitamins, essential to nutrition. Jansen and Donath isolated the water-soluble vitamin B in a pure state from rice polishings, in the form of a crystalline hydrochloride.

Geographical distribution.—The area of the endemic distribution of beriberi is coextensive, probably, with the tropical and subtropical belts. It was formerly the scourge of many of the mines and plantations of the Malay and Eastern Archipelago. It was apt to break out among the coolie gangs engaged on extensive engineering works in the tropics, such as the Panama Canal or the Congo Railway It haunted the Dutch army in Sumatra, and used to be common enough in the British armies in India. It is at home in many parts of Japan, particularly in her large, low-lying, damp, overcrowded cities. It occurs in China, the Philippines, the Eastern Peninsula, India, and

Africa. We have had accounts of a small epidemic among a group of Western Australian natives, and also among Chinese on the eastern seaboard of Australia, a continent where beriberi was formerly supposed not to exist. Some years ago beriberi broke out in a lunatic asylum in Dublin; and apparently the same disease has been seen in similar institutions in the United States and in France, and also among the Newfoundland fishermen and those on the North American coast. Tomasson has reported (1933) an epidemic in the Westman Islands, Iceland. The diet consisted of fresh fish which, even in large quantities, is deficient in vitamin B_1. Elshout and Lentjes describe a similar epidemic amongst prisoners on an island off Holland.

Epidemiology and endemiology.—*Sex, age, occupation, etc.*—Beriberi attacks both sexes. It is not uncommon in the breast-fed infants of beriberic mothers. This form, called *infantile beriberi*, may declare itself in varying ways.

Ship beriberi.—Beriberi is prevalent among the native crews, more rarely, though occasionally, among the European officers and sailors, of ships on the high seas and far away from any recent telluric influence. The crowding in the damp forecastle and the exposure incident to a sailor's life seem to be among the reasons, though not the only ones, for ship beriberi.

From 1894 up to 1920, or thereabouts, the disease was common in European crews of Swedish and Norwegian ships, which are in far better sanitary condition than British ships, and yet beriberi is comparatively rare in the latter.[1] The modern explanation of this occurrence is found in the fact that, since the year named, the crews of the Norwegian mercantile marine have been provided, under the terms of a statute, with bread baked from white flour, or a mixture of wheat and rye, so that their diet was inadequate in vitamin supply. Ship beriberi holds a place intermediate between true beriberi and scurvy, and is closely related to the disease found among the Rand miners of South Africa. A similar disease has recently been noted amongst the whale fishers of South Georgia. In Newfoundland beriberi of both forms is found at times when the diet is reduced to a regime of bread and molasses (Aykroyd).

Asylum beriberi.—The Dublin lunatic asylum, built for 1,000 inmates, had 1,500 inmates crowded into it when beriberi broke out, so that the conditions resembled those found in a ship's forecastle, already alluded to.

Ætiology.—The earliest investigators of beriberi believed that it was a degenerative multiple neuritis indistinguishable from that produced by alcohol or diphtheria, and that it was due to an infection or intoxication, and much effort has been directed to the discovery of the poison. All these theories are now a matter of history, for they have been replaced by the vitamin-deficiency theory, which it is now proposed to outline.

[1] A number of cases have been reported from H.M. ships in the Iranian Gulf.

Beriberi and Rice: Vitamin-deficiency Theory

History.—The modern conception dawned in 1881, but it was a ray of light which was rapidly extinguished. In that year Lunin, in Bunge's School in Basel, fed mice upon an artificially-composed milk and found that they would not survive. The existence of some mythical substances essential to nutrition was rediscovered by Socin in 1891 and again by Pekelharing fourteen years later; but again these conclusions were unfortunately forgotten. To C. Eijkman from 1890 onwards, and especially to Grijns, must be given the credit of proving the existence of a food-deficiency disease. In 1907 Braddon first established the correctness of Eijkman's former observations in man, and these were supported by Fraser and Stanton in Malaya and by the classical experiments of Hopkins in England—experiments directed to the recognition of the constituents of food necessary for growth.

In 1911 Funk attempted to isolate the active principle in rice-polishings and he was the first to use the term "vitamine" (afterwards altered to *vitamin*), and in 1912 he classified pellagra amongst the food-deficiency diseases. In America the recognition among workers on nutrition that vitamins are essential to life came slowly. Osborne and Mendel were early in the field and they, as well as McCollum and Davis, obtained results which differed from those of Hopkins, but the discrepancies were later found to lie in the purity of the lactose they employed for their experiments.

There still remain divergencies of opinion upon the exact interpretation of vitamin-deficiency and beriberi; according to McCarrison the toxic agent is produced during metabolism, which itself has been disordered by vitamin-B deficiency, though the toxic substances in the rice itself play no part. Recently Bernard and others have revived the bacillary theory. An organism, *Bacillus asthenogenes*, is, they assert, found in various foods, especially rice, and it becomes pathogenic in the digestive tract where it gives rise to a toxin which produces the definite classical picture of beriberi.

Thanks to the pioneer work of Eijkman (1897), Grijns, Braddon, Fraser, and Stanton, we now know that the beriberi of the Eastern Peninsula, of the Eastern Archipelago, of the Philippines, of China and of Japan, is a sequel of a diet into which overmilled rice enters as the principal element, that is, rice from which the entire pericarp and germ have been removed; and that in this pericarp and germ there is a substance essential to the proper nutrition of the nervous system of man and of many other warm-blooded vertebrates.

If a fowl be fed exclusively on "*paddi*," that is, rice from which the husk has not been removed, the fowl will thrive and very likely gain weight; but if it be fed exclusively on a diet of white rice and grain, that is, rice from which the pericarp has been completely removed, after a short time it will show signs of peripheral neuritis, lose weight, and, if the exclusive diet be persisted in, die with all the signs of a multiple peripheral neuritis. If a fowl or pigeon which, in consequence of such a diet, has begun to show signs of peripheral neuritis be given regularly some of the polishings of the rice, that is, the dust or remains of the pericarp which had been removed in the process of milling, it will gradually lose the signs of neuritis, gain in weight, and recover. The neuritis—*polyneuritis gallinarum* (or *p. columbarum*) as it is called—is evidently the result of the deprivation of some element of food essential for the proper nutrition of the nervous system of the bird, and this

element is located in the pericarp and germ of the rice grain (Figs. 48, 49). Almost miraculous recoveries in the stricken birds take place after hypodermic injection of an extract of the germ centre of wheat or other cereal.

The greater part of the rice grain is starch, and covering the central starch core there is a thin aleurone layer containing the proteid and fat constituents of the grain. Externally there is an adherent layer, the pericarp,

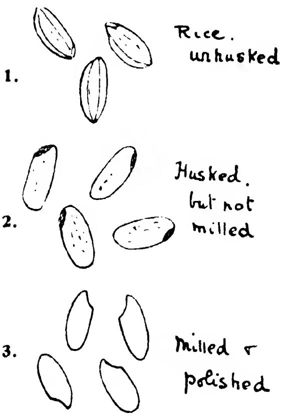


Fig. 48. — Showing the various stages in milling of the rice grain. 1, Rice grain in the natural condition enclosed in the husk or enclosing glumes; 2, After removal of the husk, but retaining the pericarp or "silver-skin" and the embryo; 3, After milling and polishing; both "silver-skin" and embryo are removed and the grains are "polished" by rubbing with talc between sheep-skins. (*After Chick and Hume, "Trans. Soc. Trop. Med. and Hyg."*)

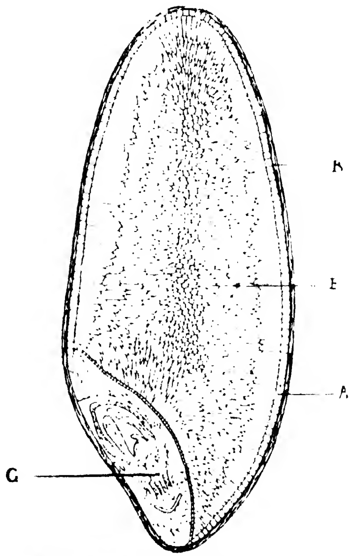


Fig. 49. Diagram of longitudinal section through a grain of wheat showing (a) aleurone layer of cells forming the outermost layer of the endosperm, removed with the pericarp during milling; (b) pericarp forming the branny envelope; (e) parenchymatous cells of the endosperm; (g) embryo or germ. (*By permission of H. M. Stationery Office, from Dr. J. M. Hamill's "Report on the Value of Bread made from Different Varieties of Wheat."*)

which varies in colour from red to white according to the variety of the rice. The pericarp contains the salts. The grain itself is covered by a husk, which is discarded as chaff.

Conditions under which rice is grown.—Rice grows normally in puddled fields in which a layer of water is allowed to remain till the grain is almost ready for reaping, and this puddled rice has a nutritic value of approximately one-third less than the same rice grown under dry rain-fed conditions; it contains also a lower content of vitamin B. The Chinese eat mostly polished rice, normally obtaining their store of vitamin B from fresh vegetables, shortage

of which has from time to time led to a great increase of beriberi in Malaya. (*See also* Chap. II, p. 35.)

Fraser and Stanton showed—and their observations have been abundantly confirmed—that the antineuritic element is located in the pericarp of the rice grain, in the aleurone layer, and in the embryo of the grain, that it is soluble in water and alcohol, is stable in acid but unstable in alkaline solutions, is thermolabile—being destroyed by a temperature of 130° C.—and that it is dialysable; that it is not a phytin or a fat, and that, although itself not containing phosphorus, the amount of phosphorus in any given rice is a reliable indication of the safety, or otherwise, of that rice as a staple article of food. Rice containing less than 0·4 per cent. of P_2O_5 they considered unsafe, and believed that its persistent use may lead to beriberi.

The polyneuritis of the fowl is identical clinically and ætiologically with the polyneuritis, called beriberi, occurring in man. For, as has been both accidentally and intentionally done, if the same experiment with rice-feeding be tried on man the result is identical—beriberi is induced. Thus, following the lines of the earlier experiments of William Fletcher, Fraser, and Stanton, Strong and Crowell conducted a series of experiments on twenty-four life-sentenced prisoners, and were able to prove (*a*) the non-communicability of the disease, and (*b*) its production in man solely by means of diet. A similar condition has been produced in rats.

The discovery of avian polyneuritis and its relationship to human beriberi has recently been the subject of much discussion. Though no reasonable doubt can exist that deprivation of the antineuritic vitamin must be regarded as the cardinal factor in both diseases, yet the diversity of their pathology and symptomatology and the uncertainty as to the rôle played by other ingredients of the *vitamin-B* complex (*see* p. 428) has made the problem more abstruse than it formerly appeared to be. McCarrison has distinguished two types of this avian disease, *polyneuritis columbarum* and *beriberi columbarum*; the former is characterized by symptoms attributable to derangement of the nervous system, the latter is distinguished by hypertrophy and dilatation of the heart, associated with fatty degeneration.

Acting on these findings, the governments of Singapore and the Federated Malay States interdicted the use of white or polished rice in their jails, lunatic asylums, schools, and hospitals, with the result that beriberi, which until then had been the cause of an enormous mortality and morbidity, has been practically banished from these institutions. Corresponding results have accrued from the same practice in Dutch Malaya, in the Philippines, and elsewhere. In India, however, as McCarrison has pointed out, the problem is not so simple. Decorticated rice is practically the staple diet of many millions in India, though beriberi is endemic only in a few circumscribed areas of Bengal and Assam, the north-east coast of Madras, the coast of Burma, and certain river valleys. The basal factor in India has to be considered as a fundamentally poor diet, whether of rice or other food grains.

True beriberi may therefore not be due to a complete absence of vitamin B_1, but to an insufficiency of it.

The period of development of beriberi in man has been determined by Fraser and Stanton as varying between eighty and ninety days.

Clear and convincing evidence has been accumulated from many lands that the substitution of under-milled for milled rice will cause beriberi to disappear in India.

Vitamin B_1 (*aneurin*) has been found to be necessary for the growth and maintenance of mammals, birds, amphibians, and even insects, and all mammals possess a definite capacity for storing and utilizing this vitamin; in the rat this suffices to last three weeks. Deprivation of vitamin B_1 has an immediate effect upon intake and metabolism, so that the malnutrition resulting from lowered intake may be responsible for many of the features of an avitaminosis, and probably it has a distinct influence upon glandular secretion. In the case of the adrenal, it causes an increase of the adrenalin content and hypertrophy of the adrenal cortex; there is also atrophy of the sexual organs. Continued vitamin-B_1 deficiency leads to a lowered resistance to bacterial infection in animals, correlated with the fall in body-temperature (Findlay).

By employing Fuller's earth and kaolin to adsorb the vitamins from autolysed yeast, the highest concentrations have been obtained. Jansen and Donath in 1926 announced the isolation of B_1 in a crystalline form, which has been further analysed by Windaus, Tscheche, and others; this led to the formula $C_{12}H_{17}ON_3S$ for the free base, of which the sulphur content is to be noted. An acid clay (pH$_5$) preparation for rice polishings is largely used in Java for the cure of beriberi and forms a satisfactory and stable preparation of vitamin B_1.

Vitamin B_1 (also known as aneurin or thiamine) is present in greatest quantity in alcoholic yeast extracts, and is extremely thermolable in that state; the synthetic product, however, is thermostable and will stand the autoclave at 120° C. for thirty minutes. The main features of experimentally-produced B_1 deficiency in man are decreased sugar-tolerance, the onset of nervous symptoms, changes in temperature, lack of accurate vision, bradycardia, and, sometimes, œdema. In endemic beriberi areas the vitamin-B_1 content of the daily diet averages about 0·5 mgm. per head. An intake of 0·75 mgm. of B_1 daily represents the border line of supply. The measurement of B_1 in human urine can be used as an index of nutritional level, and Harris, Leong and Ungley (1938) have shown that it can be thus measured by the *bradycardia method*. The excretion is graded according to the dietary intake. Thus normal persons in England excrete 20 international units per diem, while hospital patients excrete about 5 international units. Excretion of 3·5 units or less is found in beriberi, polyneuritis, and other deficiencies. The presence of pyruvic acid in the blood, urine, and *cerebro-spinal fluid can now be taken as an indication of vitamin-B_1* deficiency. The normal level of pyruvic acid in the blood is 0·5 mgm. per 100 grm. It has been found that an increased intake of B_1 will raise the level of blood-pyruvic-acid in fulminating cases of beriberi; usually 1,000–2,000 international units (2–4 mg. of crystalline vitamin) are needed in acute cases to restore normal conditions as regards this substance. Platt and Lu state that the presence of pyruvic acid, as shown by chemical tests, has been fully confirmed by isolation from the

blood of the 2 : 4 dinitrophenyl-hydrazine of pyruvic acid in sufficient amounts for analysis. In dry paraplegic beriberi, normal values are found. The amount of bisulphite-binding substance (BBS) present in the blood appears to follow the degree of vitamin B_1 deficiency. By means of these tests, there are indications that much larger doses of B_1 may be needed than have hitherto been employed. The optimum is now estimated at 20 international units per kilo body weight. Infants of one year should receive 275–300 units a day, or 1 mgm. of crystalline B_1, should be taken as sufficient.

Secondary beriberi.—The preparation of a purified crystalline vitamin B_1, which exerts distinct therapeutic action, has shed light on a great many other conditions, and it is now believed by neurologists that many other forms of neuritis are explicable on a vitamin-deficiency basis. Shattuck has been prominent in emphasizing this view, and he believes that there is a close relationship between beriberi, alcoholic polyneuritis, Korsakoff's syndrome, and Landry's paralysis.

Predisposing factors.—Certain subsidiary factors predispose towards beriberi. Given the necessary food restrictions, any lowering of the general resistance of the body may lead to the rapid development of this disease. Thus, it often makes its appearance during pregnancy, lactation, after surgical operations, or during convalescence from infectious and debilitating diseases, such as dysentery, malaria, and enteric. Breast-fed babies of mothers suffering from the disease are themselves liable to suffer from it.

Pathology.—There is very little to be said about the post-mortem appearances in beriberi which is not covered by the accepted descriptions of the lesions of peripheral neuritis. There is a degeneration of the peripheral nerves—more especially of their distal ends—and there is secondary atrophic degeneration of muscle, including that of the heart, which may be the subject of an acute fatty degeneration like that in diphtheria. Degenerative nerve-changes may be detected in the nerve-centres and throughout the implicated neurones, as in other forms of peripheral neuritis. There is invariably an involvement of the vagus, with degenerative changes in its root in the floor of the fourth ventricle. Microscopically the nerve-trunks show changes from a slight medullary degeneration to complete destruction of the nerve (Wallerian degeneration). Recent work on the nerve-changes shows that regenerative processes occur side by side with the degenerative (Fig. 50). As a rule, some fibres in the vagus and sympathetic escape ; thus the cardiac branches in the heart-muscle and the bronchial and œsophageal twigs are usually unaffected. According to Vedder, the membranes of the spinal cord are often congested and œdematous ; scattered fibres in all tracts show the same kind of changes as are found in the peripheral nerves. Degenerative changes are also found in the anterior and posterior horn cells, as well as in the sympathetic ganglia. These facts have led him to state that the condition is not a simple neuritis, but a degeneration of the entire central nervous system. If there is anything peculiar about the post-mortem appearances in beriberi, it arises from the somewhat special implication of the central and peripheral organs of the circulation—namely, dilatation of the heart, especially of the right side, and great accumulation of blood in the right heart and in the

veins. In addition, there is a marked liability in many cases to serous effusion into the pericardium, pleural cavities, peritoneum, and cellular tissue. This very marked liability to serous effusion and the tendency to cardiac dilatation may be said to be more or less distinctive of beriberi as compared with other forms of multiple neuritis. The œdema of the cardiac muscle naturally

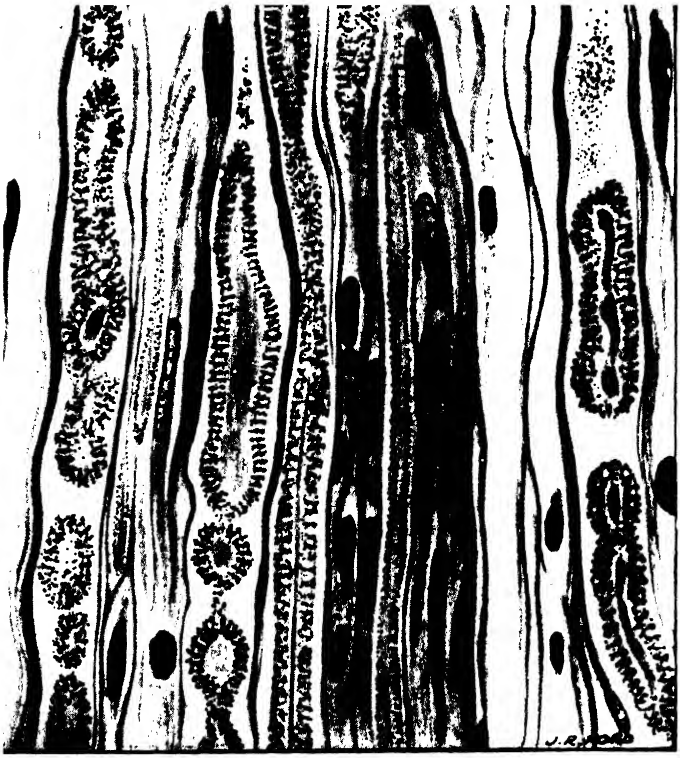


Fig. 50.—Longitudinal section of external popliteal nerve in beriberi.
One medullated fibre in centre is practically intact; the others show typical fragmentation of myelin sheath with swelling of remains of nerve-fibre.

(*Orig. case, from a preparation by Dr. A. C. Stevenson.*)

interferes with the normal fluid exchange within the fibres and therefore with its contractibility. According to Mebius, when vitamin B_1 is deficient, full muscular contractibility is impossible owing to water absorption (Wenckebach). Findlay has suggested that vitamin B_1 is an essential factor in the synthesis of animal nucleic acid by the body. Without doubt water-retention in beriberi is of the greatest importance in elucidating the mechanism of symptom production. Œdema of the lungs also is not uncommon, and has, probably, a pathology similar to that of the connective-tissue œdema. There is no nephritis. The only lesion that might be considered specific

in beriberi is the duodenitis, which may be present in acute cases during the first three weeks of the disease, though this is not invariable.

The general affection of the whole nervous system, involving the central and peripheral structures, is identical with that found in diphtheritic or alcoholic neuritis.

Fig. 51.—Ataxic or paraplegic beriberi, showing characteristic attitude. (*Orig.*)

Symptoms.—Beriberi assumes varying clinical forms according to the extent and position of the nervous lesions. As a rule, it is insidious in its onset, but it may occasionally be ushered in by acute symptoms ending fatally within a few hours without any development of symptoms referable to the nervous system. As a general rule, it is classified into two main forms, according as the peripheral nerves or the cardiovascular system are most affected. The former cases are known as paraplegic or "dry" beriberi, the latter as

œdematous or "wet" beriberi. It must be understood that in all its forms beriberi is considered to be the same disease, and that a clinical classification has but a conventional value. In all clinical forms of the disease sudden death is liable to occur from heart-failure.

Paraplegic cases.—On examining one of the paraplegic cases referred to (Fig. 51), it will be found that, besides paraplegia of greater or lesser degree, there is a certain amount of anæsthesia or of numbness of the skin, particularly of the skin over the front of the tibiæ, the dorsa of the feet, the sides of the thighs, perhaps also of the finger-tips, and of one or two areas on the arms and the trunk. Deep sensibility (Abadie's sign) elicited by compression of the Achilles tendon is usually numbed or entirely lost. The visitor may be struck with the thinness of the patient's calves and the flabby state of the gastrocnemii; and by the fact that if, whilst making the examination, he should handle these and the neighbouring muscles somewhat roughly, particularly if he should squeeze them against the underlying bones, the patient will call out in pain and try to drag the limb away. The thigh muscles may be similarly affected, and so may the thenar, the hypothenar, the plantar, and the arm muscles; like the calf muscles, these too may be wasted and flabby and exhibit fibrillary twitchings. Very probably there is a loss of fat as well, the panniculus adiposus being everywhere meagre. If tested electrically, the muscles exhibit to perfection the reaction of degeneration. If the knee reflex be tested in the usual way, after the first week of the disease there will be no response whatever; nor can any clonus be elicited, but occasionally a reflex contraction of the hamstrings may take place, giving a false impression of a knee-jerk. As a rule, all the deep reflexes are lost; but the superficial reflexes, unless in extreme conditions of paresis and muscular atrophy, are usually present and more or less active. If, in severe cases, the patient is set to button his jacket or to pick up a pin, possibly he has a difficulty about it, or perhaps he cannot; he may bungle and fumble like an advanced ataxic. The fibres of affected muscles, when struck with a patellar hammer, often contract locally in a particularly painful manner known as myœdema. There may be actual wrist-drop (Fig. 52).

There is more than ataxia, however, for the hand-grasp is so enfeebled that the patient may have a difficulty in holding his rice-bowl as well as in feeding himself. There is no tremor of the hands; and never or very rarely is there any paresis of the ocular muscles, or of the muscles of the face, of mastication, of the tongue, or of the pharynx. The sphincters and bladder operate satisfactorily, and the functions of the alimentary canal are carried on fairly well, although there is often some dyspeptic distension and oppression after food. On the patient being got out of bed and started to walk, if he is able to progress at all his gait will be markedly ataxic; but he is not ataxic merely, for, just as with the hands, it will be seen that, in addition to want of co-ordinating power, there is great muscular weakness. If

he is laid on the bed and asked to raise his legs, he is perhaps hardly able to get them off the mat, to cross them, or to place them one foot on top of the other. Very probably he is the subject of marked ankle-drop, so that he drags his toes when he attempts, in walking, to advance the foot ; he has therefore to raise the foot very high, letting it fall on the ground with a flop when he brings it down again. His ataxia and his muscular weakness, as well as the partial anæsthesia from which he suffers, force him to adopt a variety of devices to assist

Fig. 52.—Paraplegic beriberi, showing wasting of extensor muscles and wrist-drop. (*Orig.*)

him in progression. Manifestly, these patients are suffering from some form of peripheral neuritis.

The general health is good for the most part ; the tongue is clean, the bowels are fairly regular, there is no fever, and there is nothing amiss with the urine. Digestion, assimilation, and excretion go on satisfactorily.

The heart and circulation.—When the heart is examined, if the case be at all recent or moderately severe, attention is at once arrested. On inspection it may be remarked that the impulse is diffuse ; that there is epigastric pulsation ; that the carotids throb too violently ;

that there is that peculiar wobbling, pulsating movement in the jugulars that denotes tricuspid insufficiency. On percussion the præcordial area is frequently found to be enlarged, perhaps very greatly enlarged, especially to the right; and on auscultation loud bruits, usually systolic in rhythm, may be heard. Marked reduplication of the sounds, particularly of the second sound, is to be noted. The auscultator may be impressed, in a large proportion of cases, by the peculiar spacing of the intervals between the sounds. It may be hardly possible to tell by the ear alone which is the first pause and which is the second. They seem alike in point of duration; so that the sounds of the heart are, like the beats of a well-hung pendulum clock, evenly spaced, and not, as they are in health, separated by a long and a short interval like the beats of a badly-hung clock. It will also be observed that the heart is very irritable, becoming easily quickened by exertion. It will be judged, therefore, that in addition to peripheral neuritis there is serious disease in the circulatory system, particularly in its innervation; that there is dilatation of the right side of the heart, and that there is a state of relaxed arterial tension. There is a wide range in the pulse-pressure in cardiac beriberi, and it has been shown by Aalsmeer and Richter that there is almost invariably a low diastolic blood-pressure which can be influenced by the injection of adrenalin (the adrenalin effect). Pitressin raises the diastolic pressure from almost zero to 75 mm. and the venous pressure falls: this beneficial effect may last $1\frac{3}{4}$ hours.

The cardiac enlargement in human beriberi has been ascribed by Aalsmeer and Wenckebach to œdema of the heart-muscle, which results in an interference with its contractile power without disturbance of its excitability.

Wenckebach investigated a number of cases of beriberi in the Dutch East Indies and Singapore, and took special precautions to inject hardening fluid, and he was thereby able to confirm the presence of certain gross anatomical changes which are demonstrable during life by radiography. The whole of the right side of the heart is greatly enlarged, while the left remains comparatively small; the conus arteriosus takes part in the change. The large systemic veins are commonly dilated, and as much as three litres of blood escaped from the right auricle. The extrapericardial pulmonary vessels are not abnormally congested. Microscopic examination of the heart muscle after death revealed intracellular œdema, sarcolysis, and hydropic degeneration, probably primarily due to excess of lactic acid, brought about by defective oxygenation (*see* p. 428). The primary lesion is, therefore, a loss of contractibility of the heart muscle related to water retention, with consequent loss of peripheral vascular tone. The clinical picture and its response to adrenalin and pitressin, together with the lowering of diastolic pressure commonly observed is in accordance with these findings.

Aalsmeer has now employed the results of these observations as a practical test to indicate the stage of the disease and response to treatment. The diastolic pressure is known as the "minimum tone pressure," because it is the pressure registered by the sphygmomanometer at the moment when the auscultatory bruit disappears with decompression of the brachial artery. The essence of the test is that, when the diastolic pressure *is* registered, the administration of adrenalin in hypodermic doses of 1 mgm. will be found, if

observations are taken at five-minute intervals, to bring the pressure down to zero in an uncured case of beriberi. That is to say that the auscultatory murmur will persist during complete relaxation of the pressure on the artery as long as the patient is under the influence of adrenalin.

Dropsical cases (wet beriberi).—In the next bed, perhaps, to the patient whose picture has been drawn may be seen another suffering from apparently quite a different affection (Fig. 53). Instead of being wasted, his face is puffy and heavy; his lips possibly are slightly cyanosed; and his arms, hands, trunk, legs, and feet are distended with œdema. It may be thought from the œdema that it is a case of acute nephritis, but an examination of the scanty, dark-coloured urine shows that it is of high specific gravity and contains no albumin, or only a mere trace; so that the case cannot be one of acute Bright's

Fig. 53.—Wet or œdematous beriberi. (*Orig.*)

disease. Careful observation will discover that the œdema is somewhat firmer than that of nephritis and, in not a few instances, that it does not involve the scrotum. Occasionally cases are met with in which the œdema is peculiarly localized and fugitive. If attention be directed to the heart, a bruit and other evidences of dilatation of the organ and of arterial relaxation, just as in the first case, are discovered. Occasionally irregularity may be associated with slowing of the heart-beat, and it is probable that heart-block may occur in such cases. The pulse is invariably of low tension. If the lungs be examined, one may (or may not) discover signs of single or double hydrothorax, although, probably, not to a very great extent. The lungs themselves are healthy. On getting him out of bed it is found that the patient can hardly walk—partly from breathlessness, partly on account of mechanical interference by the dropsy with the movements of the legs, partly, perhaps, from some degree of paresis. He

has ankle-drop, possibly; and, if firm pressure be brought to bear on the calf-muscles through the œdema, signs of hyperæsthesia of the muscles may or may not be elicited. Knee-jerks are generally absent, and there is numbness of the shins and finger-tips. The tongue is clean, the appetite fair, and there is no fever. But there may be complaint of præcordial distress and even pain, and, as this is aggravated by a full meal, the patient eats sparingly. The amount of urine is generally very much reduced—to a few ounces, even.

In this patient, therefore, there are the same signs of peripheral neuritis and of dilatation of the heart as in the other case. In addition there is a somewhat firm œdema, which is not altogether cardiac, but, as its character and the circumstances in which it is found suggest, is probably connected partly with lesion of the nerves regulating urinary excretion, and partly with the play of transudation and absorption in the connective tissues.

Great variety in degree and combination of symptoms.—Some cases are so trifling that the patients are up and moving about with more or less freedom; other patients are so severely smitten that they lie like logs in their beds, unable to move a limb or perhaps even a finger. Some are atrophied to skeletons, others are swollen out with dropsy, and some show just sufficient dropsy to conceal the atrophy that the muscles have undergone. Though the cranial nerves above the seventh are very rarely involved, in some it will be noticed that the laryngeal muscles are paralysed, the patient being unable to speak above a whisper or to produce an explosive cough. In one or two cases the abdominal and the perineal muscles may be so profoundly paralysed that, when the cough is attempted, at most a husky expiration is produced, while the belly is bulged forward and the perineum shot downward by the sudden contraction of the muscles of expiration. In practically all cases of over a fortnight's standing the knee-jerk and tendo-Achilles reflex are absent, though the latter often persists after the former has disappeared; at the very commencement of the disease these deep reflexes are exaggerated, gradually disappearing as symptoms develop, not to reappear for months, perhaps, after the patient is well in all other respects. In some epidemic outbreaks, as, for instance, in Iraq in 1916, an irregular *pyrexia*, seldom exceeding 100° F., has been noted.

Uncertain course.—Beriberi slowly or rapidly declares itself after an incubation period of weeks or months; it may be preceded by a period of intermitting languor, aching legs, palpitations, breathlessness, slowly advancing œdema of legs or face; or the patient may wake up some morning and find that during the night he has become dropsical or paretic. Thus the disease may develop slowly or rapidly. Equally uncertain are its progress and danger; within a day or a week, or at any time during its course, it may assume fulminating malignant characters. It may completely subside in a few days, or it may drag on for months. It may get well apparently and then relapse. It may,

and generally does, clear up completely; or it may leave a dilated heart, or atrophied limb muscles with corresponding deformity. The variety in the severity, progress, and duration of beriberi is infinite: but in all cases the essential symptoms are the same—greater or less œdema, especially over the shins; muscular feebleness and hyperæsthesia, especially of the legs; numbness, especially of the front of the shins, of the finger-tips, occasionally of the lips; liability to palpitation from cardiac dilatation, and to sudden death from the same cause.

Cardiac attacks.—Most cases die from paresis and over-distention of the right heart, complicated and aggravated by œdema of the lungs, by diaphragmatic paralysis, by hydrothorax or by hydropericardium. Sudden cardiac failure (called by the Japanese "Shôshin") is often contributed to by the co-existence of pleural effusion, hydropericardium, paresis of the diaphragm, over-distension of the stomach by food or gas, and, above all, by œdema of the lungs. It can readily be understood how the establishment of any additional obstruction of this description would still further tax the dilated, enfeebled heart and determine the fatal issue.

Secondary beriberi. *Alcoholic beriberi.*—It has long been recognized that alcoholic neuritis resembles in many respects the dry form of beriberi. It resembles it so closely that in recent years the idea has gained ground that this resemblance is more than fortuitous, and that in both conditions there is an antecedent deficiency of vitamin B_1. The theoretical considerations advanced by Shattuck have led to the recognition of a variety of intestinal conditions in which polyneuritis may occur, such as gastric carcinoma, chronic intestinal obstruction, and even ulcerative colitis, and, in the opinion of some observers, all these should be included under the heading of secondary beriberi. Much work has already been done in alcoholic beriberi to confirm this interesting hypothesis. Cases have been reported of alcoholic addicts with congestive heart failure and polyneuritis who have recovered completely after treatment by rest, a high caloric diet, and vitamin B_1.

Multiple factors are probably concerned in the production of alcoholic beriberi, including defects in diet and assimilation acting in conjunction with increased tissue requirements for vitamin B_1 due to an increased rate or type of metabolism. Many cases of alcoholic neuritis have now been cured by the continued injection of vitamin B_1. Weiss and Wilkins (1936) have described the clinical syndrome of cardiac beriberi associated with alcoholic gastritis, which resembles the classical form of the disease.

It has been argued by Strauss that the *polyneuritis of pregnancy* may be of the same nature when pernicious vomiting occurs. In *diabetic neuritis*, it has been shown that the injection of vitamin B_1 exerts an influence upon carbohydrate metabolism.

Burning Feet

Synonyms.—" Chachaleh " (*Somaliland*); " Barasheh."

This is a very chronic condition which has been recognized in Malaya, British Guiana, West Africa, and Somaliland for many years. Buchanan has reported upon a series of over 100 cases from Somaliland. Pain is usually generalized, but may occur in various localities, particularly the joints, and at the back of the neck and in the shoulders.

In 82 per cent. of the patients, there was solid œdema of varying degree, whilst there was thickening of the subcutaneous tissues, especially of the thighs, abdomen, and pectoral and deltoid areas in 41 per cent. Epigastric pain is common and constipation the rule. The knee-jerks are diminished in 39 per cent. of cases. In Malaya, Kingsbury has noted sixteen cases, all, with one exception, in Southern Indians. The patients complain of severe " burning feet," usually limited to the soles, but occasionally involving the lower part of the legs. In some instances the pain was definitely worse in the mornings and was always intensified by walking. Sometimes there is a definite history of formication. This condition is considered to be a deficiency disease and in some way connected with beriberi, and to be curable by administration of vitamin B_1

War œdema ; famine œdema ; nutritional œdema.—This œdema is more pronounced than in ordinary cases of starvation, and other causes than mere lack of sufficient nutriment are at work. It is most pronounced in the feet and legs, and marked muscular weakness and alimentary-tract disturbance is common. When there was a shortage of fats, as in Central Europe during the Great War, ocular manifestations were frequently noted. In Java and Haiti a form of malnutritional œdema is prevalent among individuals whose diet is inadequate, and amongst infants fed on a preponderatingly starchy diet over a long period. In these a generalized dropsy similar to famine œdema and œdematous beriberi is observed. Though resembling œdematous beriberi, this condition is probably not due to vitamin deficiency, but to lack of albumin and fats in the food. Blood analysis reveals a deficiency in the albumin-content. The condition is curable by a liberal dietary.

Mortality.—The mortality in beriberi varies in different epidemics and in different localities. On the whole, it is greater in low than in high latitudes, in the dropsical than in the atrophic forms, in the acute than in the chronic. In some epidemics it is as high as 30 per cent. of those attacked ; in others as low as 6 per cent., or even lower.

Infantile beriberi.—This form is common in Egypt, the Philippine Islands, South China and certain Pacific Islands, and causes a high infantile death-rate. In the Philippines especially it was a terrible scourge, accounting for 16,500 deaths annually, or 28·1 per cent. of total deaths in infants under one year. It is not necessary to regard it as resembling adult beriberi in miniature, for it differs in many essentials. The disease often occurs in the rainy season. It is never seen in Caucasians and rarely in half-castes and should be regarded as strikingly a disease of poverty. It usually affects breast-fed infants of mothers who are either themselves victims of the disease or subsist

on a diet poor in vitamins. Removing the infant from the breast, or administering an extract of rice bran, usually leads to a rapid cure. The majority of observers think that the maternal milk contains some highly toxic substance, but Vedder and his American colleagues believe that the disease depends upon deficiency during uterine life and after birth of a substance in the milk which is essential to the growth and development of the child's nervous system. However, in children who die in this manner no imperfection or lack of development of the nervous system has been noted. In the most acute type it is children previously healthy, 1½ to 3 months old, who are usually attacked; after a series of convulsive attacks the child suddenly dies of acute heart-failure. In less fulminating cases, vomiting, dyspnœa, dysphagia, and aphonia may precede the heart-failure. Occasionally, chronic cases are seen in which progressive weakness and wasting, with periodical attacks of vomiting occur. In neither form has any true paralysis been noted, except that underlying the aphonia, which has been ascribed by Japanese workers to a paralysis of the left recurrent laryngeal nerve, from pressure by a dilated left auricle. According to Chan, the knee-jerks are usually absent.

Some highly interesting suggestions have been made by G. W. Bray on the inhabitants of Nauru in the Pacific with regard to this question. The death-rate from infantile beriberi in that island amongst breast-fed babies from eight to ten weeks after birth, had been approximately 30 per cent. of the total deaths during the past twelve years. The mothers themselves show no signs of dietetic deficiency, though their dietary has been shown to be singularly deficient in vitamin B. Bray has been able to demonstrate the almost instantaneous effects of partially-fermented "toddy" (the sap of the coco-nut spathe), not only in the curing, but also in the prevention of this particularly fatal malady. The dosage of "toddy" is half a drachm twice daily during the first month, one drachm twice daily during the second, three times daily from three to six months, and over that age, three to four ounces weekly. In consequence of these simple measures the disease has ceased to exist amongst the Nauruans, while the incidence of a variety of other disorders, such as bronchitis, pneumonia, furunculosis and otitis media has to a great extent abated.

It appears that this peculiarly dramatic form of infantile beriberi became prevalent since the use of "toddy" was prohibited by Government order. The therapeutic action of the toddy yeast in restoring these children is as rapid and dramatic as are similar extracts in artificially-produced polyneuritis of fowls and pigeons.

In the acute type of the disease gastro-enteric, pneumonic, and meningitic signs and symptoms prevail. There is at first disinclination for food, followed by extreme restlessness, increased epigastric swellings, paroxysmal crying and general anasarca. Vomiting is the first sign of impending death. Dyspnœa and cyanosis supervene and the child dies in convulsions (Fig. 54). The temperature is slightly raised to about 100° F. A more chronic form of the disease is also recognized, as well as an insidious form in older artificially-fed children. The diagnosis of infantile beriberi is greatly aided by blood examination; a lymphopenia is almost invariably noticed with a total absence of small lymphocytes. Bray has been able to show that the therapeutic

action of vitamin B_1 is greatly enhanced by the synergic influence of vitamin A, as in cod-liver oil, in these children.

Diagnosis.—Usually the diagnosis of beriberi is not difficult. Multiple peripheral neuritis occurring as an epidemic, or in a place or ship in which the disease has occurred on some previous occasion, may, as a rule, be set down as beriberi. Sporadic cases may be difficult to diagnose, especially if there is a history of alcoholism, of malaria or of drugging with arsenic. The presence, actual or past, of œdema—especially of œdema over the shins—and palpitations and other evidences of cardiac implication, are significant of beriberi. In the atrophic or paralytic type the *jongck* or "*squatting test*" is very useful. The patient, with his hands on top of his head, is unable to assume,

Fig. 54.—Infantile beriberi. Nauruan child in convulsions. Note general anasarca. (*Dr. G. W. Bray.*)

or rise from, a squatting position. It must be borne in mind that slighter degrees of beriberi, evidenced only by slight anæsthesia of the prætibial skin area, by slight œdema of the same region, by slight hyperæsthesia of the calf muscles, and, perhaps, by impairment or absence of knee-jerk, may be the only symptoms present. *True rheumatism is rare in the tropics.*

Meyers has introduced two new tests for the diagnosis of beriberi. The first is the development of, or increase, in an audible sound in the antecubital space after subcutaneous injection of adrenalin. The second and more important is the estimation of diuresis after the fasting patient has drunk a litre of water. Both should return to normal after administration of aneurin.

Differential diagnosis.—Cases have been diagnosed as cardiac disease, tabes dorsalis, muscular rheumatism, progressive muscular atrophy, ascending spinal paralysis, and have over and over again been relegated to that refuge for ignorance, malaria, and called

"malarial rheumatism," or "malarial paralysis," or, more pedantically, "malarial paraplegia" or "malarial neuritis," though cases of subtertian malaria rarely simulate the clinical appearance of beriberi. There should be no difficulty in distinguishing beriberi from tabes dorsalis by the Argyll-Robertson pupil and the positive Wassermann reaction. In both paraplegic beriberi and locomotor ataxia Abadie's sign (absence of pain on compressing the tendo Achillis) is present.

Beriberi can be differentiated from *alcoholic neuritis* by the tremors and mental disturbances which occur in this disease, and of which the diagnosis is generally obvious; from *arsenical neuritis* by the pigmentation, the diarrhœa, and digestive disturbances, and by the hyperkeratosis of the palms and feet that is apt to occur in this intoxication; from *chronic lead-poisoning* by the blue line upon the gums, the wasting of the muscles of the arms and legs which are most in use, the characteristic sparing of the supinator longus, and the basophilic stippling of the red blood-corpuscles; from *lathyrism* by the presence of the knee-jerks and the absence of muscular hyperaesthesia in this affection. The differential diagnosis from heart disease, chronic nephritis, and ancylostomiasis is sufficiently obvious.

There are probably other forms of polyneuritis distinct from beriberi, but which may closely simulate the latter. Possibly these infectious forms of polyneuritis are occasioned by an organism as yet undetermined. Possibly also infective forms of polyneuritis occur in association with food-deficiency. These may account for sporadic cases in which pyrexia is prominent, and also for isolated outbreaks not apparently associated with a faulty dietary.

McCarrison has noted that experimental pigeons in the pre-beriberi state—a state, that is, in which they do not exhibit any of the more alarming symptoms—are much more susceptible to extraneous infections; for instance, an infection of *B. suipestifer* may determine the onset of neuritis, while pigeons suffering from beriberi become susceptible to organisms, such as the pneumococcus, to which they are normally quite resistant. It is not unreasonable to suppose that in man a microbic factor plays a similar part in the spread of some epidemics of polyneuritis which cannot otherwise be accounted for.

In Cuba a disease resembling œdematous beriberi has been reported in patients heavily infected with the small fluke *Heterophyes* (*see* p. 899).

Prognosis.—The tendency to dilatation of the heart is the dangerous element in beriberi; it should be always before us and dominate our plans of treatment. It is wonderful how rapidly it may come on, and how quickly it may prove fatal. These sudden deaths, occurring sometimes from syncope—from instantaneous failure, as well as from the somewhat slower process of increasing over-distension—are constantly found in this disease. An absolutely favourable prognosis, therefore, ought never to be ventured on in even the mildest-looking case of beriberi, nor so long as the patient is exposed to the conditions causing the disease, nor so long as the neuritis appears to be active. That is a lesson which is often,

and sometimes painfully, borne in upon the practitioner in beriberi districts.

Evidences of grave heart-implication, such as pulsating cervical vessels, equal spacing of the intervals between the sounds audible on auscultation, enlargement of cardiac dullness, especially to the right, epigastric pulsation, a rapid feeble pulse, a distended stomach, cold extremities, cyanosis, dyspnœa, and a disproportion in the strength of the heart- and wrist-beats, are significant of danger. *Paralysis of the diaphragm, of the intercostal muscles, extensive serous effusions, very scanty urine*, are also unfavourable signs.

Vomiting.—No one can say when or how soon fatal implication of the cardiac nerves and muscle may take place, but vomiting is always an ugly and threatening symptom in beriberi. The Japanese regard the occurrence of vomiting as of fatal import. Marked dilatation of the stomach has a similar significance.

Prognosis is improved if the patient is placed on a non-beriberic diet and is treated with full doses of aneurin (that is before the heart-muscle or the cardiac or respiratory nerves are gravely degenerated).

Treatment

The first and most important thing to be attended to in the treatment of a case of beriberi is the diet. From this, rice, especially white rice, should be eliminated, and some article rich in vitamin—such as beans, peas, peanuts, barley, wheaten flour (not overmilled), or oatmeal—substituted. Apart from other considerations, rice is a bad food for beriberics; it is too bulky. Eggs are valuable sources of the anti-beriberi factor, which is not destroyed even when they are dried; they are therefore indicated. Yeast has curative properties; the extract known as *marmite* may be given in doses of 1·5 grm. daily. Animal food, including fat and milk, must enter into the dietary for general nutritional purposes. The worst cases, particularly if there is any sign of serious cardiac implication, should remain in bed; but the mild cases had better spend the greater part of the day in the open air.

In cardiac cases, with a view to diminishing to some extent the bulk of blood in the vessels and heart, the seriously affected patients should take little fluid, and keep the bowels free by means of full and repeated doses of some saline aperient. In cardiac cases small doses of digitalis or of strophanthus seem to do good. Should signs of acute cardiac distress appear, full doses—3, 4, or 5 drops of the 1-per-cent. solution—of nitroglycerin are indicated, and intravenous injections of ouabäine (a French preparation of strophanthin) $\frac{1}{240}$ gr. may be given. The dose must be repeated every quarter- or half-hour, and kept up until the threatening symptoms pass away. In suddenly developed cardiac attacks, inhalations of nitrite of amyl, pending the operation of the nitroglycerin are useful. Should signs of cardiac distension and failure persist and increase in spite of these

means, there must be no hesitation in bleeding the patient, taking, if it will flow, eight or ten ounces from the arm or, this failing for any reason, from the external jugular. Often, as the blood flows, rapid amelioration of the alarming condition sets in, and the patient is, for the time being, tided over an acute danger and given another chance. The bleeding should be repeated if the alarming symptoms recur, as they are almost sure to do. Oxygen inhalations, if available, are worth trying in cardiac attacks. Pleural and pericardial effusions should be sought for, and, if deemed to be interfering in the slightest degree with the circulation or respiration, drawn off with the aspirator.

The introduction of vitamin B_1 (aneurin) as a therapeutic agent has entirely revolutionized the treatment of beriberi, and its dramatic effects are best observed in the acute cardiac cases (*Shôshin*) when given in massive doses. Hawes, Monteiro and Smith emphasize that it is in the peracute attacks which break out without any previous warning that its effects are best seen. The maximum dosage of B_1 is 3,000 international units. Doses up to 1,000 I. U. may be given intramuscularly or intravenously. In moribund patients the injection has been made direct into the jugular vein with spectacular success. There are two crystalline preparations in use for injection, *Betaxan* (Bayer) and *Benerva* (Hoffman—La Roche). These preparations contain 2 mg., and the strong or "forte" dose contains 10 mgm., of crystalline aneurin per c.c.

By the mouth aneurin appears to be less effective. The proprietary preparation "Bemax" is widely used. *Crystoribex* (Parke, Davis & Co.) is aneurin in tablet form, and is issued in two strengths, 333 international units (equal to 1 mgm.) or 2,231·2 international units (6·7 mgm.). Benerva and Betaxan are also put up in tablet form for oral administration in doses of 1 mgm. each.

Hawes originally showed that active extracts of vitamin B_1, when given by the mouth, are destroyed in the stomach, but after the injection of a potent extract (Betaxan or Benerva) most striking therapeutic effects are noted. In cardiac or œdematous cases the patient, even when moribund, at first becomes restless after the injection, but no effect is noted in the pulse rate or in the diastolic or systolic pressures for an hour or more. If insufficient vitamin B_1 has been injected, there is a return of the dyspnœa, sudden collapse and death. In many cases, recovery is extremely dramatic. The dosage varies in different cases, and the injection is made subcutaneously or intravenously. The reaction is quantitative, and the results become apparent in the rise of systolic and diastolic blood-pressures.

Provided the patient is placed on a suitable diet and can be tided over the first fortnight, he will probably recover; but, on the other hand, should he persist in a diet of white rice, though he may get over one or two cardiac attacks, he will almost surely die in some subsequent seizure.

In the case of breast-fed beriberic infants, they should be removed from the mother and handed over to a healthy wet-nurse, or placed

on the bottle. Sometimes this is impracticable; in such cases in the Philippines a preparation of extract of rice-polishings, called "tiqui-tiqui," has the reputation of being wonderfully efficacious. It is given to the extent of 5 c.c. a day in 20-drop doses every two hours. At the end of twenty-four hours the most alarming symptoms disappear, and the child is well in three days. If the case is a very severe one, double doses should be given, and the tiqui-tiqui continued so long as there is any aphonia. The use of toddy in infantile beriberi of the Pacific has been referred to on p. 451; under modern conditions obviously the use of aneurin is indicated.

Excretion of aneurin.—The excretion of aneurin in the urine can be estimated with sufficient accuracy to be of clinical value by the thiochrome method without the use of the fluorimeter. A rapid excretion of aneurin takes place in the first three hours after subcutaneous or intramuscular injection. It is suggested that a certain amount of injected aneurin is excreted before there is time for it to be stored in the tissues (Marrack and Hoellering).

Other measures.—For the atrophy of the muscles and anaesthesia of the skin, faradization and massage should be employed as soon as the muscular hyperæsthesia has begun to subside. Hot-air baths are of considerable service. Care should be taken that permanent deformity does not occur from contraction of muscles. Foot-drop should be counteracted by Phelps's talipes splint with an elastic accumulator, and any other threatened deformity appropriately met. Relapses must not be risked by a return to the original diet or source of infection. The seaside or a sea-voyage has often a marvellously restorative effect.

Prophylaxis.—In institutions under Government control, or in conditions in which it can be successfully enforced, there should be a stringent rule against the use of overmilled rice. To legislate against the use of white rice in countries in which rice is the staple food would not be politic, and could only lead to opposition and defeat the object in view; but the authorities, by educative methods and in other ways, can do much gradually to eradicate any prejudice there may be among the natives against undermilled rice. The committee on beriberi control of the Far Eastern Association of Tropical Medicine (1925) have urged upon governments that, wherever overmilled rice forms a staple diet, steps should be taken to discourage the use of rice from which essential food factors have been removed; that safe storage should be provided for undermilled rice; and that the use of accessory foods should be encouraged.

It is most important that a practical test for rice which may cause beriberi when used as a staple article of diet should be elaborated.

As a prophylactic, *marmite*, in small ¼-oz. cubes, may be taken twice a week. Military and other expeditions should be warned that tinned meats are notably deficient in antineuritic vitamins and require the addition of other foodstuffs to protect against beriberi

as well as scurvy. Dried eggs are especially valuable, but are too expensive to be used on any extensive scale.

Contrary to what happens in scurvy, the human body does not appear to possess any appreciable reserve store of the antineuritic vitamin upon which to draw in a dietetic emergency. A constant supply, therefore, of the substance must always be maintained. The moral of this is, that for the prevention of beriberi for any population living on a restricted diet, such as soldiers and sailors on active service on land and sea, the germ and bran of wheat should be included in the manufacture of bread or biscuit where the rest of the ration consists of tinned or otherwise preserved foods.

CHAPTER XXV

PELLAGRA

Synonyms.—Mal de la Rosa; Mal Rosso; Alpine Scurvy; Asturian Rose; Psilosis Pigmentosa.

Definition and description.—An endemic disease of slow evolution, which is undoubtedly connected with a diet deficiency, characterized by a complexity of nervous, alimentary and cutaneous symptoms, which make their first appearance during the spring months (sometimes the autumn), and recur year after year at the same season, remitting more or less during the winter months. It is for the most part confined to the poorer classes, especially agricultural labourers. The more distinctive features are—(*a*) a remitting dermatitis of the exposed parts of the body; (*b*) marked emaciation; (*c*) profound depression alternating with mania; (*d*) a terminal confusional insanity.

History.—The history of pellagra is comparatively recent. In Spain it was first described by Casal in 1763, under the name of *mal de la rosa*. In Italy the disease, under the name of *Scorbuto alpino*, was described by Odoardi in 1776 and by Frapolli in 1771. The earliest mention of pellagra in France dates from 1829. We know nothing of the history of pellagra in Egypt prior to the publication of Pruner's "Topographie médicale du Caire," in 1847. In the United States of America, although there is evidence of its sporadic occurrence there for a considerable time—at least fifty years—before its nature was recognized, pellagra was first diagnosed as such in 1907. It is especially prevalent in the South-Eastern States. Dr. H. F. Harris, Health Officer of the Georgia State Board of Health, estimated that there were 50,000 cases of pellagra in his State, and in 1916 it was estimated that there were 150,000 pellagrins in the Southern United States alone, but of recent years the American outbreak has become milder in form.

Since 1912 sporadic cases of the disease have been reported in the British Isles. Many of these fall into the category of what is known as "secondary pellagra." [1]

Geographical distribution.—*Europe:* Pellagra is found in Northern Portugal, in Spain, in Italy, in the south-west of France, sparingly in Denmark and in the British Isles, in the Austrian Tyrol, in Hungary, Croatia, Dalmatia, Bosnia, Serbia, Bulgaria, Turkey, Greece, Corfu, Roumania, Bessarabia, Kherson, Poland and Transcaucasia. A few cases have been reported from Germany. *Africa:* Algeria, Tunis, Egypt, Sudan, the Red Sea coast, Rhodesia, Nyasaland,

[1] For more detailed information the reader is referred to the masterly summary by H. S. Stannus in the *Tropical Diseases Bulletin*, XXXIII, 10-12, and XXXIV, 3.

and among the Kaffirs and Zulus. It has also been recognized in Tanganyika, Kenya and on the Gold Coast. *Asia:* It has been reported from Asia Minor, Syria, North Behar and Deccan in India, the Malay States, the Philippine Islands, Japan, China and Korea. An outbreak of pellagra was recorded in Nanking in 1920 and by French observers in Szechuan. Yu has reported typical cases in Manchuria. It was especially prevalent among Turkish troops and Armenian refugees in Palestine and Syria during the Great War. *America:* Canada (since 1914), the United States, Mexico, Central America, Brazil, the Argentine, Barbadoes, Jamaica, and probably other West India Islands. *Australasia:* Pellagra has been reported from New Caledonia and in Australia (Melbourne).

History of pellagra in Great Britain.—According to Stannus, the first authentic case in Great Britain was reported by Howden in 1866, the second by Brown in 1906, and the third by Brown and Low from Shetland in 1909. In 1912 a series of six cases was investigated by Sambon and Chalmers, and in 1913 Box published his two famous cases in St. Thomas' Hospital. Since then it has come to be generally recognized that pellagra is found sporadically in lunatic asylums and in institutions, in subjects of general malnutrition. From the statistics of the Board of Control in the period 1913–1918, 45 deaths from pellagra are noted. In 1922 there were 21 deaths, mostly from the Lancashire Mental Hospital, Rainhill, and during the period 1913–1928 there have been 104 deaths from pellagra amongst asylum inmates.

Epidemiology and endemiology.—An important epidemiological feature of pellagra, in addition to those already mentioned, is the marked fluctuation of its prevalence from year to year. Thus there may be long periods of quiescence, followed by years of considerable activity during which the disease may be looked upon as a new invasion. Pellagra is not contagious. The sound may associate with the sick and remain healthy. Doctors, nurses, and attendants on pellagrins are not known to contract the disease. Pellagrous wet-nurses do not infect their charges, and attempts to transmit the disease by inoculation have failed.

Associated diseases such as ancylostomiasis, bilharziasis, tuberculosis, cœliac disease, idiopathic steatorrhœa, sprue, dysentery, and syphilis play a very important part in favouring the development of pellagra, in accelerating its course, in modifying and aggravating its symptoms, and in determining its mode of termination.

Season.—Of all diseases with marked seasonal connection, pellagra is one of the most striking in this respect. As in the case of malaria, the pellagra season varies in different localities, but is always the same in the same locality.

In Europe the disease invariably appears in manifest and epidemic form during the spring and autumn quarters, the spring outbreak being by far the more severe, the autumnal recurrence often inconspicuous or lacking. In Egypt, according to Chalmers, there is a spring invasion in April and

May, and an autumn recurrence in November. In Nyasaland, according to Stannus, pellagra seems to prevail chiefly during August, September, and October, which are the spring months in the southern hemisphere, and again, though to a less extent, in January, February, and March (fall recurrence). In the United States of America, owing to the vast extent of territory and great variety of climates, the periodical incidence of the disease is necessarily different in different sections. In the Northern States, as in Europe, the disease exhibits the usual well-marked double incidence, the spring outbreak occurring in May and June, the autumnal one in September and October. In the far south the disease may appear as early as January, and may be met with at any period of the year. In Barbados it seems to prevail more or less from May to October or November. While the wide range of pellagra throughout the world might lead one to believe that climate exerts no special influence, the very definite seasonal periodicity shows that climatic factors play an important, though indirect, part in the ætiology.

Sex.—Both sexes are liable, but in different places the disease exhibits a very different predilection for the one or other sex in accordance with the occupations and habits of the people. In the United States it is said to be more prevalent in women from 17 to 40 years of age; the debilitating effects of menstruation, pregnancy, and lactation are held to be predisposing and determining factors.

Age.—Pellagra was considered to be a disease of middle age, the majority of cases occurring between twenty and fifty. Sambon has shown that within the endemic centres children are attacked, and that no age is exempt, he having seen the characteristic symptoms in a woman over one hundred years old and in infants of barely three months.

Occupation.—The disease prevails most of all among field-labourers. The inhabitants of towns, even of those in the very heart of intensely pellagrous districts, enjoy an immunity similar to that of town-inhabitants as regards malaria. Felix pointed out that pellagra is quite exceptional among the Jews, who, as a race, rarely engage in agriculture.

The flooding of some of the Southern States in America by the overflowing of the Mississippi in 1927 afforded a practical example of the application of modern laboratory findings. Pellagra, though common in these States, is dependent to a great extent on economic conditions. The diet of molasses and cornmeal contains very little of the PP factor, and only when the financial conditions allow can milk, eggs, etc., be purchased. The failure of the cotton crop means poverty, reduced food, and pellagra.

Ætiology.—Pellagra has been ascribed to the most varied causes, such as insolation, poverty, insanitary dwellings, syphilis, irritant oils, bad weather, alcohol, garlic, onions, maize. Some have regarded it as "sunstroke of the skin." "Sun disease" was an old popular name, and certainly the skin manifestations of pellagra are influenced by the action of the direct rays of the sun. This was proved experimentally, first by Gherardini, who varied the limits of the eruption by systematically displacing parts of the clothing; and later by Hameau, who obtained differently shaped patches of erythema

by means of gloves fenestrated in different ways. In smallpox, and also in other exanthemata, we notice a decided influence of light, more particularly of the actinic rays, on the production of their skin eruptions. Although light may influence the eruption in pellagra, this is no adequate reason for concluding that insolation is the cause of the disease, any more than that it is the cause of smallpox, and in fact other stimuli applied to the skin, such as pressure or exposure to X-rays, may cause the appearance of a pellagrous dermatitis. In support of the sunlight hypothesis, certain experiments on the effect of sunlight on animals fed on a too restricted (unphysiological) diet have been advanced; but it is evident that this cannot be the whole, though it may be part of, the truth.

Many theories have in the past been advanced for the causation of pellagra, and the evidence in favour of a deficiency of food or an unbalanced dietary greatly outweighs other considerations.

Pellagra and maize.—The general opinion is that pellagra appeared soon after the introduction of maize into Europe, and that it advanced *pari passu* with the extension of maize cultivation and with the more general adoption of the new cereal as an article of food. For these and other reasons maize is still held by many to be the causative agent of pellagra, just as a certain condition of rye is known to be the cause of ergotism; and, as in the latter case, various theories have been propounded to explain the operation of the assumed cause.

Lombroso and Bellardini, in 1871, first advanced the theory that the prevalence of pellagra in Italy was due to the consumption of diseased maize, and their ideas subsequently formed the basis for public measures against the disease in that country, as well as in Southern Europe. In Lower Egypt, as pointed out by Wilson, pellagra is common, as compared to Upper Egypt, and it is in the Delta that the proportion of land given over to maize is considerably higher than that under wheat, so the distribution of pellagra in that country corresponds to the area of maize cultivation. In 1921 Wilson pointed out the importance of hard labour as a predisposing cause of pellagra. The consumption of maize by large communities does not necessarily imply the existence of pellagra as an endemic disease; this is the case in Mexico and in some parts of India.

While it is certainly true that pellagra occurs commonly in those countries in which maize flour enters largely into the composition of bread, in this manner forming the staple article of diet, yet it is difficult on this basis to account satisfactorily for the sporadic cases of this disease which have been reported from the British Isles, Germany, Poland, and China, where maize does not enter the dietary.

Already in 1845 Roussel, a very discriminating French physician, pointed out that the history of the spread of pellagra in Europe is the history of the introduction of maize as a staple food, and he first clearly realized the value of milk in the treatment of pellagra.

Shelley in Nyasaland thought pellagra to be due to absorption of a toxin which produces a neuritis of certain peripheral nerves, since the skin lesions are most marked in the areas supplied by the lower cervical, the lower lumbar and first sacral nerve roots.

It is necessary also to refer to the work of Leutsky, who endeavoured to prove that the pellagrous syndrome was due to insufficient mineral components in maize as a staple article of diet.

Deeks in 1912, and Funk in the same year, suggested that pellagra is a

disease produced by a deficiency in diet. Pellagra, together with beriberi and scurvy, they considered were "food-deficiency" diseases and due to lack of certain vitamins in the food. The experiments conducted by Goldberger and Wheeler in America were in favour of such a hypothesis.

In 1914 they fed a squad of eleven prisoners on a rich carbohydrate diet deficient in proteins. After five months, six of the number developed cutaneous symptoms suggestive of pellagra (the first lesions consisted of an erythematous patch on the scrotum). An experiment in the converse direction also proved successful, for, by substituting a rich protein diet for one consisting in great part of carbohydrates, they succeeded in banishing pellagra from an orphanage asylum in which up to that time the disease had been in evidence. In 1917 Goldberger successfully disposed of Sambon's infection theory[1] by obtaining sixteen volunteers who attempted to infect themselves by ingesting skin scales and naso-pharyngeal secretions over a period of six months. During this trying period they remained quite healthy.

Biological protein value of dietary (B.P.V.).—The results of the Commission which investigated the prevalence of pellagra among the Turkish prisoners in Egypt (1919) tended to show that the error of metabolism in the disease is manifested in a primary deficiency of "biological proteins." A large number of cases occurred among the Turks, and later among the Germans. In the former, out of 105,468 prisoners, 9,257 cases were recorded, while there were 79 German and Austrian cases out of 7,600 prisoners. During the year 1919, 1,617 deaths occurred among the Turks from this cause, and 6 among the Germans. Wilson and Roaf, members of the Commission, suggested that in a susceptible subject, whose protein assimilation is sufficient for all needs while at rest, pellagra may develop when bodily needs are increased by physical labour, or when his faculty of metabolism has been vitiated by damage to the powers of alimentary absorption, as, for instance, by bacillary dysentery or other intestinal disease ; in these cases a considerable loss of protein-absorption power was noted, the power being reduced to less than 67 per cent. It was noted further that, as long as the prisoners were at rest, pellagra was in abeyance, but broke out immediately they were subjected to any exertion. It would appear also from these observations that, in an individual whose balance of protein metabolism has been undermined for a sufficiently long period, subsequent feeding with a suitable dietary may not prevent the appearance of pellagrous symptoms.

Corkhill has shown that in the Arabs of the Sudan pellagra is common among the millet-eaters, and the period of maximum intensity is in the hot, dry season when no protein food is obtainable.

Vitamin B_2—Goldberger, who at first believed that an amino-acid deficiency was the cause of pellagra, in 1922 obtained evidence pointing in another direction. Having accidentally discovered that yeast was effective in preventing and treating blacktongue in dogs, a disease then thought to be analogous to pellagra, Goldberger and Tanner tried the effect of yeast as a prophylactic in the human disease. It was found that 30 grm. daily of brewers' yeast gave complete protection. This would supply less than 15 grm. protein, and later it was found that an acid preparation of yeast, which contained very little protein-nitrogen, in doses of 15 grm. daily was equally effective. A PP (pellagra-preventive) factor was therefore postulated in yeast and other foodstuffs. As the result of these investigations on man

[1] Sambon had endeavoured to prove that pellagra was an insect-borne disease conveyed to man by species of *Simulium*. This theory was short-lived.

and experimental work on rats, Goldberger and his colleagues were able to identify the PP factor with a vitamin in the yeast-vitamin complex differing from the antineuritic vitamin in its stability to heat and its distribution in foodstuffs. The vitamin is now known as B_2 and by some authorities in America as vitamin G. The therapeutic value of yeast in pellagra is acknowledged. In rats, too, the lack of vitamin B_2 produces a symmetrical dermatitis on the paws and body not unlike that of pellagra, but there is no evidence of degeneration of the central nervous system (Findlay and Stern) and it is now attributed to another fraction of the complex, known as *Vitamin* B_6 (*see* p. 430).

There are those who see in the clinical manifestations of pellagra evidences of hypo-adrenalism. Thus Sclare considers this to be the primary factor, with superadded vitamin deficiency. Stannus, on the other hand, has suggested that the origin of the evil may be located in the stomach, representing a further analogy between pellagra and pernicious anæmia. In the latter the fault lies in a defective secretion of the intrinsic factor by the pyloric gland organ; in pellagra there may be default of the intrinsic or the extrinsic factor, or of both.

The relationship of pellagra to blacktongue in dogs.—Chittenden and Underhill observed that in dogs given a diet of wheat-flour biscuits, peas, and cotton-seed oil, a pathological syndrome was produced reminiscent of pellagra in man. In periods of from one to six months the dogs showed necrosis of the tongue accompanied by blood-stained diarrhœa. This disease, also known as canine typhus, is well known to veterinarians. Pellagra and blacktongue appear to have a similar geographical distribution in the United States. It was proved later by Goldberger and Wheeler that the blacktongue preventive factor was the thermostable, which linked it up with "rat" and human pellagra. Now Aykroyd and Roscoe have pointed out that the distribution in foodstuffs of the PP factor, the blacktongue preventive factor, and vitamin B_2 showed fair agreement.

Conclusion.—That pellagra is unquestionably associated with a poor and monotonous diet and its appearance can be prevented by suitable dietary alterations, more especially by the addition of foods rich in the vitamin-B complex, was proved conclusively. The missing factor has been found to be in part of the vitamin-B_2 complex represented by nicotinic acid and nicotinamide (*see* p. 429).

Pathology.—The pathological features essential to pellagra are usually obscured by complicating diseases, such as bacillary dysentery and tuberculosis. The morbid anatomy is neither constant nor characteristic; for this the chronicity of the disease, the variety of the symptoms, and the many intercurrent affections which may arise are responsible.

A constant and striking feature is the great emaciation. The viscera show chronic degenerative changes, particularly fatty degeneration, and a characteristic deep pigmentation. The intestinal walls are greatly attenuated through wasting of their muscular coat, while at the same time the mucous lining is hyperæmic and, not infrequently, ulcerated. The liver and spleen are usually atrophied. The suprarenal capsules may be atrophied and the cortex may be black, while the medulla is whitish in colour, but may be the seat of hæmorrhages.

There may be actual wasting of the brain, the ventricles being distended by an excess of fluid. In the cord the lateral columns and the crossed pyramidal tract are especially implicated, but the direct cerebellar tracts usually

escape. The anterior cornual cells are frequently atrophied and deeply pigmented. The posterior columns do not escape, the median portion being often degenerated. The degenerative changes in the lateral columns are chiefly in the middle and lower thirds of the dorsal region, those of the posterior columns principally in the cervical and upper dorsal region. The cerebro-spinal fluid shows little change ; there is usually no increase in the globulins.

Mott remarked, as to the changes in the cerebrum, cerebellum, pons, medulla, and spinal cord, that in none of the sections is there any evidence of meningeal or perivascular infiltration with lymphocytes, plasma cells, or polymorphonuclear leucocytes. All the changes were like those produced by a chronic toxæmia, possibly in the manner already suggested above. The posterior spinal ganglia cells show, in varying degree, a pronounced chromatolysis, swelling of cells, and disappearance of Nissl's granules, and all the anterior-horn cells and their homologues in the medulla and pons a varying degree of perinuclear chromatolysis. There is usually marked chromatolysis of the cells of Clarke's columns. The Betz cells of the cortex and the cells of Purkinje showed similar changes, but in a less degree. In short, the changes in the central nervous system resemble those of central neuritis (Adolf Meyer) or subacute combined degeneration of the cord.

Shattuck has recently drawn attention to the similarity of the central nervous lesions to those of subacute combined degeneration of the cord, as originally suggested by E. J. Wood and also emphasized by S. A. Wilson. Perivascular pigmentation of the cerebrum, cerebellum, and midbrain has also been described and was observed by the Editor in autopsies in Egypt during 1916. Although the distribution of the lesions in pellagra differs from that commonly seen in beriberi, the changes appear to be similar. The evidence points to a close ætiological relationship between beriberi, Korsakoff's syndrome, pellagra, central neuritis, and subacute combined degeneration of the cord.

Central neuritis was first described by H. H. Scott on sugar estates in Jamaica, and similar conditions have been found in Sierra Leone and Nigeria. The central nervous lesions are widespread ; the peripheral nerves are de-myelinated and the posterior root ganglia of the spinal cord show degenerative changes. The medulla, cerebellum, basal ganglia, and optic nerves are also affected. The analogy with pellagra is a close one.

Symptoms.—The course of pellagra is generally long. The disease does not pursue any regular course, but one of repeated exacerbations and periods of quiescence. The initial symptoms are composed of mingled psychical and digestive disturbances. It is possible that these may recur for years without the appearance of skin eruptions. The patient is pale, has a peculiar staring look, and complains of headache, giddiness, and vague but often severe pains in the back and joints. His character changes ; he becomes irritable, and at the same time stupid and morose.

The earliest signs of a pellagrous tendency are difficult to define, as there are probably a great many people who suffer from chronic ill-health and are in the pre-pellagrous stage. Such individuals manifest themselves by a peculiar stomatitis with erosions at the angles of the mouth (angular stomatitis) (Plate XI). There is often also an atrophic condition of the lips (*perlèche*). The Editor drew attention to this

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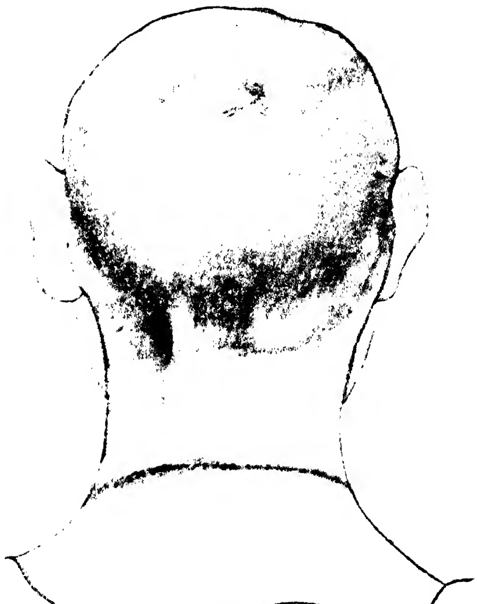

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Fig. 1. Characteristic inflamed tongue of acute pellagra with angular stomatitis.
Fig. 2. Early pellagrous rash, with cellular infiltration and pigmentation.
Fig. 3. Typical pellagrous rash over occiput and mastoid processes, with formation of "rosary" round neck.

PELLAGRA.

Plate XII

condition in Ceylon in 1912 in prisoners who had been fed on a dietary of dried fish. Since that time, it has been noted by Landor and Pallister in Malaya, by Nicholls in Ceylon, by Moore in Nigeria, and by the Editor in cases from Rhodesia. The tongue is glazed, with loss of the filiform papillæ, and the angles of the mouth are excorciated (Plate XX, Fig. 1, facing p. 592), as shown by Stannus in 1912. Often there are eye symptoms, with conjunctivitis and lachrymation. Sometimes there is a roughening of the skin (toadskin or *phrynoderma*) on the elbows and knees, and a scrotal rash. This larval form of pellagra is not uncommon in England, where many cases go unrecognized. Nicotinic acid is remarkably efficacious in these cases. The gums may be swollen and bleed easily, a condition which gave rise to the name "Alpine scurvy." There may be eructations of gas, nausea, and vomiting. The appetite is variable. The epigastric region and, sometimes, the lower part of the abdomen, are tense and painful. Constipation may be present, but in many instances there is diarrhœa of pale fermenting stools resembling those of sprue and cases of this nature are by no means uncommon in English practice.

The skin symptoms.—Most observers regard the skin lesions of pellagra as the earliest manifestation of the disease, but possibly they are symptomatic of some chronic and grave constitutional disturbance. At first an erythema, not unlike a severe sunburn, is observable on parts of the body which are, as a rule, unclothed and exposed to the sun (Plate XI). The eruption is symmetrical and characteristic. It appears suddenly, first on the back of the hands and feet, then on the forearms, legs, chest, neck, face, and, it may be, on the scrotum or on the female genitalia. The patches of erythema are irregular in outline and intensity. Very characteristic are the symmetrical patches behind the mastoid processes, a ring or collar round the neck, and a butterfly patch over the bridge of the nose resembling lupus erythematosus. The affected area is swollen and tense, and the seat of burning or itching sensations which become particularly acute on exposure to the sun. The character of the eruption is well shown in the Plates. In the case shown in Plate XI it was limited on the feet by the outline of the Turkish slippers the patient wore. The congestion disappears completely, but temporarily, on pressure. Petechiæ are common on the affected parts, and blebs with clear, opaque, or blood-stained contents of feebly alkaline reaction may form. The eruption usually lasts about a fortnight, and is followed by desquamation, which leaves the skin rough, thickened, and permanently stained a light sepia colour. This is especially marked on the back of the hands and on the elbows, and forms recognizable evidences of the disease. It is on account of this roughness of the affected skin that the disease is called "pellagra," an Italian word (from *pelle* (skin) and *agra* (rough)).

Stannus has suggested, as a result of the work of Sir Thomas Lewis on the blood-vessels of the human skin and their responses, that the actual skin lesions in pellagra are due to the liberation of histamine and

its action upon the blood-vessels, and that the mechanism of the production of the affections of the mucous membranes is of a similar nature.

The burning sensation in the soles of the feet and palms of the hands which is such a common symptom in pellagra may be ascribed to the same cause (*see* p. 450).

An obstruction to the sebaceous ducts on the alæ nasi produces a peculiar sulphur-flaked appearance of the skin in that region. Naturally these appearances differ considerably in different races. What is an erythema in the European becomes a blackish or purplish patch on the skin of a negro. In olive-skinned races pellagrous patches are of a sepia colour.

Implication of the *nervous system* is indicated by tremor of the tongue, exaggerated deep reflexes, and mid-dorsal spinal tenderness. Coarse tremors of the extremities, especially of the head and the hands, are frequently noted and become more marked as the disease progresses. Muscular cramps may occur, and a definite ankle-clonus is often seen. The patient suffers from obstinate sleeplessness, occasionally from uncontrollable sleepiness. He experiences great weakness, especially in the lower extremities, and is subject to peculiar attacks of giddiness, with a tendency to fall forwards or backwards. Another characteristic symptom is a feeling of burning in the palms of the hands and the soles of the feet. Chvostek's sign, mechanical irritability of the facial nerves, is said to be present in the majority of cases. A very characteristic symptom is pyrosis or a burning sensation down the œsophagus. This frequently creates the idea in the patient's mind that his food does not agree with him, or even that attempts are being made to poison him. The anæmia of pellagra is usually of the secondary variety. The erythrocytes and hæmoglobin are diminished to a limited extent in the uncomplicated disease. As a rule there is a definite lymphocytosis, but it cannot be said that, although usually disturbed, the differential leucocyte-count is constant or characteristic. The gastric juice is deficient in hydrochloric acid. An indirect van den Bergh test is given in all cases. There is no change in the corpuscular fragility and the plasma albumin is lightly less than normal.

After the disappearance of the eruption, atrophic patches of skin remain in the interdigital clefts, and these, together with muscular wasting, give the appearance of washerwoman's fingers. The hands, in fact, are aged out of proportion to the rest of the body. The nails become atrophied and brittle.

As a rule there is no marked permanent elevation of temperature, but periods of slight fever occur at irregular intervals.

Two or three months after onset the symptoms abate and, although the affected skin areas remain dark-coloured and rough, the disease appears to be arrested. Next spring, however, the whole series of phenomena recurs in a more severe form. The eruption assumes a

darker colour. The depression of spirits deepens into melancholia, which may have maniacal interludes, with a peculiar tendency to suicide, especially by drowning. The general feeling of weakness increases ; the patient loses weight and is unable to work ; his gait becomes uncertain and somewhat of the spastic paraplegic type. The tongue is tremulous. The pains in the head and back become very acute, and there may be lightning pains, cramps, twitchings, tremors, and even epileptiform seizures of the cortical type. Diarrhœa may now be troublesome.

For several years the disease may thus recur in the spring with increasing severity. The patient becomes greatly emaciated, paralytic, and completely demented. Helpless, bedridden, suffering from incontinence of urine and uncontrollable diarrhœa, covered with bedsores, and neglected, he dies from exhaustion or from some intercurrent disease.

The duration of pellagra is exceedingly variable. It may last only two or three years ; it usually extends to ten, fifteen, or more.

Cases differ considerably. The obscure forms are probably much more common than the fully declared disease. This fact was formerly abundantly recognized, and they were known—somewhat incongruously—as *pellagra sine pellagra*. In some the nervous symptoms predominate, in others the gastro-intestinal : in others again the cutaneous. Forms of hyperæsthesia may occur in different regions of the body. Ocular symptoms, such as ptosis, diplopia, amblyopia, mydriasis, are not uncommon. The urine is generally alkaline and may rapidly become ammoniacal. It may also contain tube-casts and traces of albumin and, usually, indican. An interesting aspect of the urinary excretion has recently been explored in the excretion of coproporphyrin. As emphasized by Beckh and Ellinger, this is specially noticeable in the alcoholic variety, and now Spies, Cooper and Blankenhorn have shown that the amount of coproporphyrin in the urine is proportional to the nicotinic acid intake.

Pellagra in childhood is very apt to be overlooked, especially in native races. The children become irritable, their skin and hair tend to lose their normal colour and glossiness, and there may be attacks of diarrhœa with transient œdema of the hands, feet, and face. After the end of ten days or so pigmented patches appear on the skin of the extensor surfaces about the ankles, knees, wrists, and elbows, and these blackened patches appear first where there is any focus of irritation or pressure.

A very acute form has been described under the name of "pellagra typhus." In this there are intense prostration, high temperature, muttering delirium, pronounced nervous tremor, generalized rigidity, and convulsions. In extensive outbreaks of pellagra, such as occurred among the Turks during the Great War, cases of this description may be comparatively common.

It has been estimated that in Italy from 4 to 10 per cent. of the pellagrins become permanently insane. Similarly, in the United States of America the pellagrins are becoming numerous in the lunatic asylums. The type of insanity is usually a most profound melancholia with a suicidal tendency; cases may resemble in their clinical features general paralysis of the insane.

Epileptiform convulsions may rarely occur. The time of the appearance of mental symptoms is subject to the widest variation. They may be seen as primary symptoms, or may occur during convalescence. The mental aberrations may be characterized by profound dementia, hallucinations, and the occurrence of katatonia. As a rule, restlessness, vertigo, and insomnia anticipate the characteristic melancholia. Not only may pellagra lead to insanity, but those insane from other causes are very liable to develop pellagrous manifestations. Goldberger found that in certain asylums in the United States the number of lunatics developing pellagra each year was a constant proportion of the total. In England, pellagra has been noted in lunatic asylums since 1913. Watson, in a review of the pellagra cases in the Rainhill Asylum, Lancashire, found that they had been resident in the institution from six months to several years.

Pellagra due to voluntary restrictions of diet has been recognized by several observers during recent years. Mook and Weiss have seen the typical clinical picture of pellagra in a young woman on a slimming diet; Mumford, Carley and others have seen it in mature women who, for some faddist cult, had been subsisting on an unbalanced dietary; Guthrie, Green, Walker and Wheeler have reported similar phenomena in patients on a ketogenic regime.

Secondary pellagra has now come to be recognized as a clinical entity. In nearly all its manifestations, pellagra is associated with some organic lesion in the gastro-intestinal tract, such as œsophageal stricture, carcinoma of the stomach, pyloric ulcer, or pyloric stenosis, carcinoma of the ileum, stricture of the rectum, rectal polyposis, suppurating hydatid cyst, chronic amœbic dysentery, cœliac disease, or idiopathic steatorrhœa; the Editor has recorded one striking case in association with sprue. "Alcoholic pellagra" is the designation applied by American observers to the disease as it occurs in chronic alcoholics, which appears to be not uncommon in that country. It has been suggested by Stannus that an explanation of pellagrous manifestations in relationship with these various conditions, is that gastritis is the one common factor to them all, and it supports the hypothesis that, primarily, in pellagra there may be a fault of the intrinsic factor.

Diagnosis.—Of course, doubtful cases are occasionally encountered, but a localized erythema associated with nervous symptoms, particularly mental symptoms, great debility, and seasonal recurrence, in a person in or coming from a pellagrous district, can hardly be confounded with any other disease. The rash may be mistaken for

acrodynia, erythema multiforme, dermatitis venenata, eczema solare, trade dermatitis, lupus erythematosus, syphilis, or poison-ivy dermatitis; the gastro-intestinal disturbance and the glossitis for sprue; while the nervous manifestations have to be differentiated from hysteria, general paralysis of the insane, ergotism, and lathyrism. In old people with arterio-sclerotic changes and accompanying mental symptoms, there may be lesions of hands and feet which may be a source of confusion. "Pink disease" in children may also be mistaken for pellagra, as the distribution of the skin lesions is very similar.

Treatment.—Since the end of the Great War and the formulation of the *biological protein theory*, many workers, notably Goldberger and Wheeler, noted that improvement in the pellagrous lesions, and even in the nervous involvement, followed a liberal dietary rich in proteins and in vitamins. Then ensued a period in which liver and yeast extracts, notably Marmite, were given an extensive trial, but it was generally conceded that, though the therapeutic secret was locked up in the vitamin-B complex, vitamin B_1, as exemplified by the modern purified preparations, was not the main factor concerned.

In 1937 Elvehjem, Madden, Strong, and Wooley reported the cure of blacktongue in dogs by the administration of nicotamide prepared from yeast. Shortly afterwards Spies, Cooper, and Blankenhorn recorded the successful treatment of four human pellagra cases. These patients were in hospital and received a controlled basal diet, upon which alone symptoms had shown no improvement. Relatively large doses of *nicotinic acid* were given—40–80 mgm. by injection, or 200–1,500 mgm. by the mouth within a period of twenty-four hours. Almost simultaneously Fouts, Helmer, Lepkovsky, and Jukes reported the cure of four cases of "alcoholic pellagra" treated on the same lines, there being improvement in the mental condition, the stomatitis, and the intestinal disorder, as well as a cure of the dermatitis. Spies, Bean, and Stone (1938) then published a series of 73 cases of endemic pellagra and 99 of "subclinical pellagra," and stated that they had not observed a single acute case that had not responded promptly to nicotinic-acid therapy. Also in a special study by Spies, Aring, Gelperin, and Stone of 60 cases showing acute mental disorder, improvement was observed within periods of ten hours to six days after nicotinic-acid medication, the daily dosage being 500–1,000 mgm. by mouth, or 100 mgm. intravenously. Further confirmation was soon at hand from Matthews who studied 13 cases of classical endemic pellagra maintained on a pellagra dietary. These favourable results in American pellagra have received a considerable degree of confirmation in the hands of Alport, Ghaligoungui, and Hanna in the Egyptian disease, and also of Ellinger, Hassan, and Taha (1937). They treated 15 cases with nicotamide (Merck), the dose being 1 grm. daily by the mouth or 0·5 grm. by subcutaneous injection, and found that dizziness and throbbing of the head were more liable to ensue after the latter procedure. On the

whole they found that acute inflammation of the tongue and aphthous ulceration of the mouth subsided in five to seven days, and the sense of taste returned in the same time; in one case colic supervened almost immediately, suggesting intolerance. Thus nicotamide affected great improvement in the acute mucous-membrane lesions, as well as in the skin condition; on the other hand, chronic skin lesions or friction areas and chronic changes in the tongue were only slightly affected. The appetite, mental condition and general physical health were all improved. Grant and Spies also record that ptyalism, Vincent's infection and coproporphyrinuria also disappeared, and Hawksley found great change in the follicular hyperkeratosis on and around the naso-lalial folds.

In contrast to the success recorded above, it is necessary to state that Schmidt and Sydenstricker have recorded failure to cure 15 chronic pellagrins with nicotinic acid, while 17 control cases, receiving 60 grm. of brewer's yeast, all improved after six weeks. (The doses of nicotinic acid—100 mgm. *twice weekly*—were much smaller than in the former studies.)

The Editor, with Ransford, has recorded (1938) in London almost instantaneous improvement on nicotinic-acid therapy (150 mgm. daily) in patients with glossitis, angular stomatitis, emaciation and diarrhœa, who for some reason had been living on a restricted dietary and had hitherto been regarded as suffering from sprue. They have drawn attention to the necessity of recognizing as pellagrous conditions many obscure mouth lesions in residents in England.

The evidence that nicotinic acid is a specific cure for pellagra and for the somewhat similar nutritional diseases produced by maize diets in dogs and pigs (Chick, Macrae, Martin, and Martin) thus appears to be conclusive, and it is now reasonable to ascribe the curative value of liver extracts and yeast which was formerly observed in pellagra to the nicotinic acid which they contain. Ruffin and Smith (1937) found that, whereas crude liver products were effective in relatively small doses in canine blacktongue and in pellagra, larger amounts of more purified extracts were ineffective. These observations, which suggest that a combination of two substances is needed to correct deficiencies in diets which induce blacktongue and pellagra, are difficult to reconcile with the curative effect of such simple substances as nicotinic acid and nicotinamide.

It is obviously important to ascertain the content of nicotinic acid or its amide in maize. Estimations published by Swaminathan show that, while maize is the poorest of a series of grains examined (1.5 mgm. nicotinic acid per 100 grm.), wheat (5·33 mgm.) is the richest.

The reactions to nicotinic acid in normal individuals are tingling and increased warmth over the malar regions and neck. Sometimes nausea, vomiting and abdominal cramps may ensue. Nicotinic acid and nicotinamide are now put up in a convenient form by a number of firms—in tablets of 30 to 50 mgm. each. Burroughs, Wellcome tablets

(50 mgm.) are given three times daily (150 mgm.) for ten to fourteen days in some mild cases, and double that quantity (300 mgm.) in more severe ones. Overdosage causes some tingling and numbness of the tongue, and also in the lower jaw along the course of the inferior dental nerve. Nicotinic acid treatment should, of course, be backed up by a liberal protein dietary and, if possible, should be controlled by estimation of the urinary coproporphyrins.

Recently Spies, Aring, Gelperin and Bean submitted 60 cases with mental manifestations to treatment with nicotinic acid and *coramine* (the diethylamide of nicotinic acid). These cases showed loss of memory, delirium, mania, or depression ; some had a paranoid reaction. Recovery took place in all cases within six days. Korsakoff's psychosis and maniac depressions were not influenced. Coramine is given in doses of 2–5 c.c. daily by the mouth to a total of 20–50 c.c.

Prophylaxis.—In view of the volume and importance of recent researches in this field, it is evident that the prophylaxis of pellagra is bound up in public-health measures and especially in ensuring a well-balanced protein dietary. Whether pellagra can be prevented by the prophylactic administration of nicotinic acid remains to be seen.

CHAPTER XXVI

SCURVY IN THE TROPICS

EPIDEMICS of this disease are apt to occur among gangs of coolies and labourers who are fed on an unsuitable dietary ; this is especially the case in natives recruited for labour purposes and fed upon dried cereals and preserved foods, who previously had been in the habit, in their own villages, of consuming large quantities of fresh vegetables and fruit such as bananas.

Ætiology.—Scurvy is a food-deficiency disease. It is produced, not by general starvation, but by the absence of an accessory food factor, or vitamin, which can now be prepared synthetically and is known as ascorbic acid. This body (p. 430) is present in all fresh vegetables, including swedes, turnips, and onions, and in fresh fruit, especially the orange and lemon. It is very sensitive to prolonged heat and drying, and therefore is absent from tinned fruits and vegetables, and from dried legumes such as peas and beans, but reappears directly these latter are induced to germinate. Yeast, fresh meat, and milk contain only small quantities of the antiscorbutic vitamin, and, curious to relate, according to Chick and Hume, preserved *lime*-juice little or none at all, while preserved lemon-juice is rich in this substance.

The antiscorbutic factor is soluble in water and in alcohol, and will pass through dialysing parchment, or a porcelain filter, without appreciable loss. It is more stable in acid than in alkaline media. In 1919 Aschoff and Koch first propounded that scurvy has a primary deficiency due to lack of cement substance, and later Wolbach demonstrated that deposition of collagen in the organization of the blood-clots in the state of absolute scorbutus was referable to the administration of vitamin C. *Ascorbic acid* administered orally or parentally to scorbutic guinea-pigs has been shown by Menkin and Wolbach to induce reparative processes, as demonstrated by the renewal of dentine formation in the incisor teeth and the deposition of osteoid matrix and chondromucin at the costo-chondral junction, and these changes present additional proof that ascorbic acid is the same as vitamin C. One milligramme of ascorbic acid is sufficient to protect a guinea-pig against scurvy.

Vitamin C (ascorbic acid or cevitamic acid) not only regulates the colloidal condition of intercellular substances, but also has a respiratory function in the cell. Human milk contains more ascorbic acid than does cow's ; on an adequate diet it contains 60–80 mgm. per litre, on an inadequate one 10–20 mgm. It is important to note that potatoes, when stored, rapidly lose their vitamin-C content. Normal individuals and newly-born infants have a reserve of the vitamin. The normal output of an adult is 33 mgm. per diem ; when large doses of ascorbic acid are given there is a rise of urinary excretion, and the degree of response indicates the degree of saturation. In scorbutic persons the amount of ascorbic acid excreted is diminished.

Symptoms.—The onset of scurvy is insidious, with loss of weight, progressive weakness and pallor, and a feeling of stiffness in the leg muscles. The gums soon become affected with a swelling and sponginess of the alveolar margin. As the disease progresses the gums present fungating masses projecting beyond the teeth, which loosen and fall out. The tongue swells, the salivary and lymphatic glands enlarge, and the breath becomes very foul. The skin becomes dry and rough, and very soon subcutaneous petechiæ form on the limbs and trunk, commencing *around the hair follicles*, especially on the thigh (Fig. 55). Hæmorrhages occur into the muscles of the thigh and into the knee-joint. Very painful effusions under the periosteum form irregular nodes, which may break down and ulcerate. Œdema of the ankles is common, and hæmoptysis or hæmatemesis may occur. Any injury is apt to cause a hæmorrhage.

Together with these objective symptoms the patient experiences cardiac distress, with irregularity of the pulse and hæmic bruits at the apex. The

Fig. 55.—Scurvy rash in sprue, showing distribution of petechiæ round hair follicles. (*Orig.*)

urine is generally loaded with albumin. On the other hand, the digestive system is not disturbed, constipation being more constant than diarrhœa. The psychical disturbances are pronounced. Headache is noted early, and delirium supervenes in the later stages. In the most advanced cases the jaw-bones generally become necrotic.

In the young the formation of a "scurvy rosary" at the junction of the costal cartilages, and separation of the epiphyses of the long bones, may occur in a variety known as infantile scurvy, or Barlow's disease.

Scurvy occurs endemically in the mine-workers on the Rand. Darling and others have noted that a certain proportion of these cases are distinct in a clinical sense from those seen elsewhere. In this variety, known as *Rand scurvy*, the spongy gums and loose teeth that occur in the classical type of the disease may be absent, while the heart undergoes primary hypertrophy, with subsequent dilatation suggestive of beriberi, though the neuritic symptoms of beriberi are absent, and the knee-jerks are actually exaggerated. Rand scurvy tends to occur especially among gangs of native labourers when fed upon an unsuitable dietary; this is particularly the case in natives from the Congo and tropical Africa, who have been in the habit of consuming large quantities of fresh vegetables and fruits, and who, when at work in the mines, are fed upon dried cereals and preserved foods. The number of these cases is very large indeed. Donaldson reports that in 1920 more than 200 cases of

scurvy were treated in one hospital, of which number one-third occurred within three months of entering the mines. It has been found that scurvy in these natives predisposes to all kinds of bacterial infections, and especially to pneumonia. In cases where the diet is deficient but not entirely lacking in vitamin C, actual symptoms of scurvy may not manifest themselves, but such individuals are very prone to bacterial infections owing to degenerative changes in the bone-marrow.

Diagnosis.—To diagnose scurvy under modern conditions is no difficult matter; but care must be taken to distinguish mild cases from pyorrhœa alveolaris. A method of diagnosing scurvy in the early stages, especially in children, has been devised by Hess. The arm-band of a sphygmomanometer is placed upon the arm and inflated till the pressure reaches 90 mm., and the venous circulation is shut off. This pressure should be maintained for three minutes and then released. As soon as the cyanosis fades, an examination should be made for the petechial spots which may confirm the diagnosis of scurvy. This test depends on increased fragility of the capillary endothelium. Rotter introduced an *intradermal test* with dichlorphenol-indophenol, which can now be procured in standardized and sterilized solution. An intradermal needle is used and 1/100 c.c. of the dye-solution is injected. The time taken for decolorization of the tissues is a measure of their vitamin content. This method is a rapid clinical test, so that disappearance of the dye in five minutes suggests tissue saturation, but longer than ten minutes a vitamin-C deficiency.

Treatment.—This is chiefly dietetic. The disease, if recognized early, readily yields to a diet composed of fresh fruit and vegetables; when these are unprocurable, fresh meat can be substituted, but is by no means so satisfactory. Germinating peas are useful when fresh vegetables are unobtainable. The following method of using peas and other pulses is recommended by Chick and Hume:

Suggested Methods of preparing Peas, Lentils, or other Pulses for the Prevention of Scurvy, in the Absence of Fresh Vegetables

1. The dry seeds must be whole, retaining the original seed-coat, and not milled or decorticated.

2. They must be soaked in water for several hours; the time necessary depends on the temperature—24 hours at 50° to 60° F., and 12 hours or less at 90° F.

3. The water must then be drained away and the peas, etc., allowed to remain in the moist condition with access of air. They will then germinate and the small rootlet grow out. . . . This germination will take 48 hours at 50° to 60° F., and 12 to 24 hours at 80° F.

Soaking.—The peas or other pulses, placed in a *clean* sack, should be steeped in a trough, barrel, or other suitable vessel, full of clean water, and should be occasionally stirred. The sack and trough, etc., should be large enough to allow for the swelling of the peas to about three times their original size. In a hot climate 6 to 12 hours should suffice for this soaking.

Germination.—The peas should be lifted out of the water and spread out to a *depth not exceeding 2 to 3 inches* in a trough or other vessel with sides and bottom porous or well perforated with holes; this is to allow *complete* access of air. *The seeds must be kept in a moist atmosphere,* by covering with damp cloth or sacking, which is sprinkled (by hand or automatically)

as often as is required to keep the peas thoroughly moist underneath. . . . *All the vessels should be clean.*

4. *It is important that the germinated pulses should be cooked and eaten as soon as possible after germination, and should not be allowed to become dry again ;* in that case the antiscorbutic properties acquired during the process of germination will again be destroyed. The pulses should not be cooked longer than necessary.

Raw onions are very valuable antiscorbutics, and raw potatoes and swedes have a very definite curative value. Canned vegetables, with the exception of canned tomatoes, are useless.

In the case of natives, the most valuable antiscorbutic foods are orange, lemon, and pawpaw juice, sweet potatoes, and green mealies. Incompletely fermented beer, such as the Kaffir beer, made from germinating grain, is said to be of considerable value, but this is doubtful.

Vaughan, Hunter and others have now reported brilliant successes in the treatment of scurvy with minute doses of synthetic ascorbic acid (*see* p. 430).

Several cases have now been reported upon by Schultzer, Parsons, Harris, Ray, and Szent-Györgyi ; 40 mgm. of ascorbic acid have been given intravenously to an adult for ten days with success ; to infants 30–60 mgm. daily by the mouth for about fourteen days. It has been shown by Harris and Ray that the average amount of ascorbic acid in human milk is 0·056 mgm. per c.c. The average daily requirements are probably about 25 mgm.

Prophylaxis.—The prevention of scurvy consists in following the directions laid down, together with attention to oral hygiene. It has been pointed out that the main factor in the production of scurvy in native African races is the prolonged over-cooking[1] and steaming of food, especially of vegetables. It is, therefore, important that in gangs of unmarried natives efficient cooks should be appointed. As a general rule, the food cooked by native women is much more hygienic and palatable than that prepared by the men.

Wherever possible, in mines or tropical camps, native gardens should be established. Men threatened with scurvy should be given light work only.

[1] When cabbage is cooked for one hour at temperatures ranging from 80–100° C. the leaves lose 90 per cent. of their antiscorbutic value.

Section III.—ABDOMINAL DISEASES

CHAPTER XXVII

CHOLERA

Definition.—Cholera (χοληρροια = flow of bile) is an acute, infectious, epidemic disease, characterized by profuse purging and vomiting of a colourless serous material, by muscular cramps, suppression of urine, algidity and collapse, the presence of the cholera vibrio in the intestine, and by a high mortality.

History and geographical distribution.—It is probable that from remotest antiquity cholera has been endemic in Lower Bengal, and has from time to time spread as an epidemic over the rest of India. In 1817 it began to extend all over Asia, eastwards as far as Peiping and Japan, southwards to Mauritius, and westwards to Syria and the eastern shores of the Caspian. Stopping short at Astrakhan in 1825, it did not on that occasion invade Europe. Since 1830, when cholera first visited Europe, there have been at least five European epidemics—1848-51, 1851-55, 1865-74, 1884-86, and 1892-95. Minor epidemics have occurred in Europe since, but have been restricted in area. During the Balkan War of 1913, and in the course of the Great War, especially in the Balkans and in Iraq, there were many outbreaks of cholera but the disease did not extend as an epidemic beyond the actual seat of war.

The 1870-73 epidemic practically spared Great Britain, but it crossed the Atlantic and, entering by way of Jamaica and New Orleans, raged for a time in the United States.

From a study of the march of these epidemics it is to be concluded that cholera reaches Europe by three distinct routes—(1) via Afghanistan, Persia, the Caspian Sea, and the Volga valley; (2) via the Persian Gulf, Syria, Asia Minor, Turkey in Europe, and the Mediterranean; (3) via the Red Sea, Egypt, and the Mediterranean.

Epidemiology and endemiology.—Cholera follows the great routes of human intercourse, and is conveyed chiefly by man—probably in its principal extensions by man alone—from place to place. In India, during religious gatherings, hundreds of thousands of human beings are collected together under highly insanitary conditions—as at the Hurdwar and Mecca pilgrimages. Cholera breaks out among the devotees, who, when they separate, carry the disease along with them as they proceed towards their homes, infecting the people of places they pass through. The Hedjaz has, for the last 90 years, been the post of relay of cholera in the rate of progress from the Far

East towards the West. During that period there have been 27 outbreaks. In India cholera appears to spread from its home in Lower Bengal over the northern and western, central, and southern provinces in a series of waves of two to four years' duration. Cholera never travels faster than a man can travel; but in modern times, owing to the increased speed of locomotion and the increased amount of travel, epidemics advance more rapidly and pursue a more erratic course than they did sixty years ago. On the other hand, isolated countries, such as the Andaman Islands, Australia, New Zealand, the Pacific islands, the Cape Province, and the West Coast of Africa, have so far escaped.

There are two types of outbreaks of cholera, according as the general water-supply is contaminated or when such contamination is localized to certain wells, cisterns, etc. In the former instance the outbreak is explosive and cases occur simultaneously in all parts of the city and disappear again with almost equal suddenness. As an example of the first type of outbreak, the Hamburg epidemic of 1892 is the most instructive. During a period of only two months cholera attacked 17,000 persons causing 8,605 deaths in a population of 600,000. The water-supply of Hamburg was taken directly from the river, while the adjoining city, Altona (population 140,000) filtered its water from the river by a slow sand process. Although Altona lies further down the river and is contaminated with the sewage of Hamburg, yet the deaths in Altona were only 2·1 per mille as against 13·4 per mille for Hamburg. To illustrate the second type of transmission, there is the well-known incident of the Broad Street pump in 1854. This was the first definite proof of the association of cholera with water. It was noted that cholera was ten times more prevalent in Golden Square than in other parts of London, and it was noted that the cases increased in the neighbourhood of the Broad Street well. The employees of a factory where the well water was used had a large number of cases, while an adjoining brewery which had a well of its own did not furnish a single case.

Rogers believes that the condition necessary for the spread of cholera in India is an absolute humidity of over 0·400, and that by watching the climatic conditions influencing the seasonal and annual incidence of cholera, increased or epidemic prevalence should usually be foreseen in time to enable steps to be taken to lessen its spread.

The forecasting of cholera epidemics has now become an actual possibility. Based upon statistics which have been subjected to modern scientific analysis, an outbreak can be predicted two to three months ahead. All the coefficients of correlation between the measure of cholera incidence and other variables to the highest possible order have been taken into consideration. The association of high relative humidity with high temperature, accompanied by intermittent rains, forms the most favourable atmosphere for the development of the disease, and the presence of endemic centres from which epidemics may at any time spring, must also be accepted.

D'Herelle made the interesting suggestion that the rise and fall of epidemics of cholera is due to the amount of bacteriophage produced.

Patients in whose stools no bacteriophage appears die of cholera. Those cases in whom the bacteriophage is strong from the outset, rapidly recover. This substance, it is said, can also be demonstrated in well water. Indian observers have recently found, on analysis according to the periodogram method, that in South India cholera occurs in a periodicity of six years.

Ætiology. *Discovery of the comma bacillus, or vibrio.*—The cholera vibrio was first discovered by Koch in Egypt in 1883; this discovery he confirmed in Calcutta in 1884 by finding it in every case of the

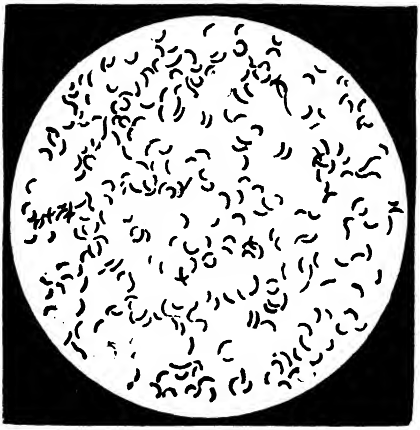


Fig. 56.—Cholera bacillus. Agar culture: 24 hours' growth. × 1,000. (*Muir and Ritchie.*)

disease he examined. His observations have since been abundantly confirmed.

Description of the cholera bacillus.—The comma bacillus (Fig. 56) is a very minute organism, 1·5 to 2 μ in length by 0·5 to 0·6 μ in diameter—about half the length and twice the thickness of the tubercle bacillus. It is generally slightly curved like a comma; hence its name. After appropriate staining, flagella can be distinguished at each end or at one end only—sometimes one, sometimes (though less frequently) two. These flagella, though of considerable length—from one to five times that of the body of the bacillus—owing to their extreme tenuity are difficult to see in ordinary preparations. They are not always present during the entire life of the parasite. In virtue of this appendage the bacillus exhibits very active spirillum-like movements. The individual bacilli when stained show darker parts at the ends or at the centre, suggesting spore-formation. Sometimes in cultures two or more bacilli are united, in which case an S-shaped body is the result; or it may happen that several bacilli are thus united, producing a spirillar appearance.

The comma bacillus is easily stained by watery solutions of fuchsin, or by Löffler's method, dried cover-glass films being used. It is decolorized by Gram.

The bacillus grows best in alkaline media at a temperature of from 30° to 40° C. Growth is arrested below 15° or above 42° C.; a temperature over 50° C. kills the bacillus. Meat broth, blood-serum, nutrient gelatin, and potato are all suitable culture media. It multiplies rapidly without curdling in milk. It dies rapidly in distilled water; it survives longer if salt be added to the water—for instance, 285 days in sea-water.

In gelatin plates it grows readily as minute white colonies, irregular in shape, and granular, with surrounding liquefaction, into which the colonies of vibrios sink as into funnel-shaped depressions. In gelatin stab-cultures the growth at first is most active near the surface; later, as growth proceeds along the needle track, a finger-shaped liquefaction results, which in time extends to the sides of the tube. In older cultures involution forms are common; they may die out after five or six weeks.

Agar is not liquefied, and in it the cultivations retain their vitality longer. On potato, at 20 to 30° C., the culture appears as a thin, brownish, porcelain-like film. In broth some of the bacilli form a scum on the surface; others, falling in masses to the bottom, leave the body of the liquid clear. As a rule, the cholera vibrio does not produce hæmolysis, if blood be added to the medium it grows on, such as agar, after twenty-four hours' incubation. The test is best performed in a fluid medium by adding varying amounts, from 1 c.c. downwards, of a three days' culture in alkaline broth to 1 c.c. of a 5-per-cent. suspension of goat's corpuscles and then thoroughly mixing. After incubation for two hours the tubes are placed in the ice-chest overnight and read the next day. With the solutions of sugars (1-per-cent.) usually employed, the vibrio produces acid, without gas-formation, in glucose, mannite, saccharose, and maltose. The fermentation of lactose, with acid production, occurs two to three days later.

Although taken together, and in conjunction with the morphological appearances, these culture characters are fairly distinctive, nevertheless certain other vibrios, such as Finkler's spirillum, behave very similarly; and, as the morphology and behaviour of these paracholera organisms are very much like those of the cholera vibrio, a mistake is easily made. The cholera-red reaction is obtained by the addition of pure sulphuric acid to a culture in 1-per-cent. peptone solution.

The true Koch's vibrio may further be recognized by employing an artificial immune rabbit's serum, which will agglutinate the organism microscopically up to a titre of 1 : 12,000. This is the most satisfactory method of identifying the cultures, and is, in fact, the final test.

The true cholera vibrio gives a positive cholera red and a negative Voges-Proskauer reaction.

Is the comma bacillus the germ of cholera?—Until recently a considerable amount of hesitation was felt by many authorities in accepting the cholera vibrio as the true germ-cause of cholera.

Certain organisms, known as the paracholera, or inagglutinable vibrios (Finkler-Prior and El-Tor), resemble the cholera vibrio minutely. Organisms found in fowl cholera, in decomposed cheese, and in river water also resemble it very closely, but, as they behave somewhat differently in the serological sense, they must be considered to be biologically distinct. Cultures of cholera vibrios have been swallowed many times by way of experiment, and, although in some instances diarrhœa has resulted, in only one case has true cholera been produced; furthermore, a few cases have been described which

from a clinical point of view appear to be cholera, but in which the comma bacillus has not been discovered after a most careful bacteriological examination. Probably for the production of cholera several conditions are necessary, of which the comma bacillus is only one. The difficulty of producing true cholera in lower animals by the administration of cholera cultures has exercised the minds of many, especially in the days following Koch's discovery, but more recently cholera-like symptoms have been produced in ground-squirrels by administering cultures of the organisms in alkaline media.

The exact significance of the non-agglutinating vibrios still remains a matter of debate. By employing an "open bowl" method of enrichment of the fæces in a cholera district, Tomb and Maitra have been able to show that 35 per cent. of the inhabitants are chronic carriers of non-agglutinating vibrios, and they have proved to their satisfaction that the agglutinability is mainly an artificial property developed and fixed in the organism by laboratory cultivation. When inseminated into water in a tank under natural conditions, agglutinating vibrios in cholera stools changed in twelve to fourteen hours to the non-agglutinating form. It is therefore possible that agglutinating vibrios are merely different phases of the same organism. Doorenbos has brought forward evidence that the El-Tor vibrio and other vibrios which behave somewhat differently are, in fact, the true cholera vibrio contaminated with bacteriophage. The virulence of the cholera vibrio can be exalted by passage through guinea-pigs and successive culturing of the peritoneal exudate of intraperitoneally injected animals alternating with culture media growth inoculations. Such a fixed virus, the virulence of which cannot be exalted, forms the material used by Haffkine for his cholera vaccine.

Gardner and Venkatraman (1935) have made a most thorough examination of the whole cholera-group question. They found that heat-stable antigens are divisible into (*a*) a considerable number of specific antigens which are best demonstrated by O group sera and H-O suspensions, which serve as a basis of classification into O subgroups, and (*b*) a non-specific component which is demonstrable with O sera and O suspensions.

(1) The first subgroup contains all the standard cholera vibrios, and is considered to be the only class known to cause epidemics of cholera.

(2) The hæmolytic "El Tor" vibrios are serologically diverse, and this term should be reserved for those with the same O component as the standard cholera vibrios.

(3) For identification of the undoubted cholera vibrios a standard subgroup (1) O serum is recommended in conjunction with the hæmolytic test, and this should contain both the main and subsidiary antigens of the subgroup.

(4) As a working rule, it is suggested that bacteriological proof of a cholera organism should rest on the isolation of non-hæmolytic vibrio with the specific O antigen of subgroup (1).

Toxins.—Filtered cultures of the cholera vibrio have little toxic action; the virus is apparently liberated by the disintegration of individual organisms. Dead cultures, when given by the mouth, produce no effect, unless the intestinal epithelium is injured. The toxic bodies are mostly destroyed at 60° C.; when ground up and frozen by means of liquid air, an extract of high toxicity to laboratory animals, if injected intravenously, is obtained. In the human body the organism multiplies in the small intestine, and liberates an endo-

toxin which is responsible for the desquamation of the endothelium and other manifestations of the disease.

Phan was able to produce the clinical phenomena of cholera in guinea-pigs by injecting cholera endotoxin in doses of 0·05–0·1 c.c. in the neighbourhood of the splanchnic nerves. Similar results were obtained in rabbits by injecting doses of 0·2 c.c.

Methods of infection.—Infected material is conveyed from sick to healthy persons, either by water, food, or infected linen. Milk, raw fruit, and vegetables and other uncooked foods are all able to serve as media for the transference of the vibrio. Clothing, if kept moist, can retain the infectivity for days and weeks. Greig has shown in India that in stools kept in the dark at room temperatures, the average life of the vibrio is about eight days. When dried the vibrio only survives for a few hours. In water the vibrio of cholera remains viable for a considerable time. In reservoir water they live about two weeks, but some grossly contaminated streams, such as the Ganges, are unfavourable to their survival.

Cholera carriers.—Patients who have recovered from cholera may continue to excrete the vibrio irregularly for weeks ; as a rule 90 per cent. become free from infection in 14 days and 99 per cent. in a month. The existence of apparently healthy cholera carriers has now come to be recognized. In some instances 20 per cent. of those in immediate contact with cholera patients have become carriers. While cholera was prevalent in Manila, McLaughlin found 6 to 7 per cent. of carriers amongst healthy persons living in infected districts. A healthy cholera carrier may continue to excrete the vibrio for two months. *Yatren*, or *quinoxyl* (*see* p. 540) is said to be an efficient drug in curing the carrier state ; 1·5–2 grm., given daily *per os*, causes the disappearance of the vibrios within two to five days.

Immunity.—The guinea-pig or rabbit may easily be immunized against the cholera vibrio by repeated intraperitoneal injections of killed cultures of the vibrio. The blood-serum thus obtained shows marked agglutinative properties in a high titre towards cultures of the organism. Furthermore, this serum, when injected into a non-immune animal, has marked protective power against even four or five times the lethal dose of organisms. When this happens, active bacteriolysis takes place, a phenomenon known as Pfeiffer's reaction. The test is performed as follows :

A loopful of a young agar-culture of the vibrio is added to 1 c.c. of bouillon containing 0·001 c.c. of anti-cholera serum, and is injected into the peritoneal cavity of a young guinea-pig ; by means of capillary tubes inserted into the peritoneum, the peritoneal fluid is examined microscopically every few minutes. If the original culture was a true cholera vibrio, the organisms break up into globules ; if not, no change takes place. The inoculation of animals by cholera cultures produces an immune serum which is remarkable for its high agglutinating power, the titre going as high as 1 : 20,000. For an agglutination test to prove that vibrios isolated from the stools are true

cholera, a serum of a titre of 1 : 4000 should be used. This is the surest proof that a suspected organism is cholera.

Pathology.—Rigor mortis occurs early and persists for a considerable time. Curious movements of the limbs may take place in consequence of post-mortem muscular contractions. On dissection the most characteristic pathological appearances in cholera are those connected with the circulation and with the intestinal tract.

If death occurred during the algid stage, the surface presents a shrunken and livid appearance. On opening the body, all the tissues are found to be abnormally dry. The muscles are dark and firm ; sometimes one or more of them are discovered to be ruptured—evidently from the violence of the cramps during life. The right side of the heart and the systemic veins are full of dark, thick, and imperfectly coagulated blood which tends to cling to the inner surface of the vessels. Fibrinous clots, extending into the vessels, may be found in the right heart. The lungs are usually anæmic, dry, and shrunken ; occasionally they may be congested and œdematous. The pulmonary arteries are distended with blood, the pulmonary veins empty. The liver is generally loaded with blood ; the gall-bladder full of bile ; the spleen small. Like all the other serous cavities, the peritoneum contains no fluid, its surface being dry and sticky. The outer surface of the bowel has generally a diffuse rosy-red, occasionally an injected appearance. On opening the bowel it is found to contain a larger or smaller amount of the characteristic rice-water material, occasionally blood. The mucous membrane of the stomach and intestine is generally pinkish from congestion, or there may be irregularly congested or arborescent patches of injection here and there throughout its extent.

If death occurred during the stage of reaction, the tissues are moist ; the venous system is less congested ; the lungs are probably congested and œdematous, perhaps inflamed. Very probably there are evidences of extensive enteritis.

Greig has shown that the gall-bladder and biliary passages are frequently invaded by the cholera vibrio and that, as in the case of enteric, this viscus may act as a reservoir of infection. Occasionally, according to the same authority, cholera may be a septicæmia ; the vibrios have been demonstrated in the substance of the lung and kidneys, and in the spleen ; they may be excreted in the urine (8 times in 55 cases—Greig).

On microscopical examination of the contents of the bowel during the acute stage of the disease the comma bacillus, in most cases, may be demonstrated. Usually it is in great abundance ; occasionally it occurs in almost a pure culture in the upper part of the small intestine and duodenum, but it may be very scarce in the large gut. Sections of the intestine show the vibrio lying on and between the epithelial cells of the villi and glands.

Bannerjee and Dutta have demonstrated focal necrosis in the kidneys with hyaline changes and sclerotic atrophy. There are also marked changes in the convoluted tubules.

Symptoms.—An attack of cholera commences in one of two ways : either it may supervene in the course of what appears to be an ordinary case of diarrhœa, or it may come on suddenly and without any well-marked prodromal stage. During cholera epidemics diarrhœa is unusually prevalent. It is a common observation that at such times

an attack of this latter nature, after a day or two, may assume the characters of true cholera. The preliminary looseness in such cases is called the "premonitory diarrhœa." Whether this looseness is specially related to the subsequent attack, or is of an ordinary catarrhal or bilious type and acts simply by predisposing to the specific disease, has not been determined. Possibly, owing to a catarrhal condition—in itself non-specific—the resisting power of the mucous membrane is impaired; possibly, in diarrhœa, the large amount of fluid in the gut affords a favourable medium for the cholera germ to multiply in. Besides diarrhœa, other prodromata, such as languor, depression of spirits, noises in the ears, etc., are sometimes noted.

When true cholera sets in, profuse watery stools, painless or associated with griping, and at first fæcal in character, pour, one after the other, from the patient. Quickly the stools lose their fæcal character, becoming colourless or, rather, like thin rice-water containing small white flocculi in suspension. Enormous quantities—pints—of this material are generally passed by the patient. Presently vomiting, also profuse, at first perhaps of food, but very soon of the same rice-water description, supervenes. Cramps of an agonizing character attack the extremities and abdomen: the implicated muscles stand out like rigid bars, or are thrown into lumps from the violence of the contractions. The patient may rapidly pass into a state of collapse. In consequence principally of the loss of fluid by the diarrhœa and vomiting, the soft parts shrink, the cheeks fall in, the nose becomes pinched and thin, the eyes sunken, and the skin of the fingers shrivelled like a washerwoman's. The surface of the body becomes cold, livid, and bedewed with a clammy sweat; the urine and bile are suppressed; respiration is rapid and shallow: the breath is cold, and the voice is sunk to a whisper. The pulse soon becomes thready, weak, and rapid, and then, after coming and going and feebly fluttering, may disappear entirely. The surface temperature sinks several degrees below normal to 93° or 94° F.; whilst that in the rectum may be several degrees above normal 101° to 105° F. The patient is now restless, tossing about uneasily, throwing his arms from side to side, feebly complaining of intense thirst and of a burning feeling in the chest, and racked with cramps. Although apathetic, the mind generally remains clear. In other instances the patient may wander or may pass into a comatose state.

This, the "algid stage" of cholera, may terminate in one of three ways—in death, in rapid convalescence, or in febrile reaction.

When death from collapse supervenes, it may do so at any time from two to thirty hours from the commencement of the seizure, usually in from ten to twelve. On the other hand, the gradual cessation of vomiting and purging, the reappearance of the pulse at the wrist, and the return of some warmth to the surface may herald convalescence. In such a case, after many hours' absence, the secretion of urine returns, and in a few days the patient may be practically well

again. Usually, however, a condition known as the "stage of reaction" gradually supervenes on the algid stage.

Reaction: cholera typhoid.—When the patient enters on this stage the surface of the body becomes warmer, the pulse returns, the face fills out, restlessness disappears, urine may be secreted, and the motions diminish in number and amount, becoming bilious at the same time. Coincidently with the subsidence of the more urgent symptoms of the algid stage and this general improvement in the appearance of the patient, a febrile condition of greater or less severity may develop. Minor degrees of this reaction generally subside in a few hours; but in more severe cases the febrile state becomes aggravated, and a condition in many respects closely resembling typhoid fever, "cholera typhoid," ensues.

During the stage of reaction death may occur from a variety of complications—from pneumonia, from enteritis and diarrhœa, from asthenia, or from such effects of uræmic poisoning as coma and convulsions.

In cholera there is a considerable variety in the character of the symptoms and in their severity, both as regards individual cases and as regards different epidemics. It is generally stated that during an epidemic the earlier cases are the more severe, those occurring towards the end of the epidemic being on the whole milder.

Ambulatory cases occur during all epidemics. Such cases are characterized by diarrhœa and malaise merely; there is never complete suppression of urine, the diarrhœa never loses its bilious character, and it is not accompanied by cramps. The attack gradually subsides without developing a subsequent stage of reaction.

Cholera sicca.—A very fatal type is that known as "cholera sicca." In these cases, though there is no, or very little, diarrhœa or vomiting, collapse sets in so rapidly that the patient is quickly overpowered as by an overwhelming dose of some poison, and dies in a few hours without purging or any attempt at reaction.

Hyperpyrexia is an occasional though rare occurrence in cholera. In such cases the axillary temperature may rise to 107° F., the rectal temperature perhaps to 109° F. These cases also are almost invariably fatal.

Sequelæ.—Cholera is apt to be followed by a variety of more or less important sequelæ, such as anæmia, mental and physical debility, insomnia, chronic entero-colitis, nephritis, different forms of pulmonary inflammation, parotitis apt to end in abscess, ulceration of the corneæ, bedsores, and gangrene of different parts of the body. Jaundice occurs at times, and is said to be of the gravest import. Pregnant women almost invariably miscarry, the fœtus showing evidences of cholera.

Mortality.—The average case-mortality in cholera amounts to about 50 per cent. Some epidemics are more deadly than others. As already mentioned, the mortality is greater in the earlier than in the later stages of an epidemic. To the old, the very young, the

pregnant, the subjects of grave organic disease—particularly of the liver, kidneys, and heart—the dissipated, the underfed, and the feeble, the danger is very great.

Diagnosis.—During the height of an epidemic the diagnosis of cholera is generally easy; the profuse rice-water discharges, the collapse, the cold clammy skin, the cyanosis, the shrunken features, shrivelled fingers and toes, the feeble husky voice, the cold breath, the cramps, and the suppression of urine, together with the high rate of mortality, are generally sufficiently distinctive. But in the first cases of some outbreaks of diarrhœa, which may or may not turn out to be cholera, and the true nature of which, for obvious reasons, it is of importance to determine, correct diagnosis, though urgently required, may not be so easily attained.

Symptoms resembling true cholera may supervene in the course of an ordinary severe *diarrhœa*, and are very usual in cholera nostras, in mushroom poisoning, in ptomaine poisoning, in the early stages of trichinosis, and in a certain type of pernicious malarial fever, as well as in fulminating bacillary dysentery. In none of these, however, is the mortality so high as in cholera. It may be laid down, therefore, that epidemic diarrhœa attended by a case-mortality of over 50 per cent. is cholera.

In other forms of diarrhœa it is rare for the stools to be persistently so entirely devoid of biliary colouring matter as they are in cholera. A careful inspection of the stools sometimes yields valuable information in other ways. Thus in mushroom poisoning, fragments and spores of the mushrooms which caused the catharsis may be seen; in trichinosis the microscope may detect the adult trichina. In choleraic malarial attacks, the presence of the malaria parasite in the blood, the periodicity of the symptoms, their amenability to quinine, together with the character of the prevailing epidemic, generally combine to guide to a correct diagnosis.

The detection of the comma vibrio in the stools is regarded as a positive indication of cholera. It would be rash, however, to affirm that a negative result from bacteriological examination of a single case rules out cholera. Moreover, such examinations, to be trustworthy, have to be made by a skilled bacteriologist.

In the first place the stools should be examined microscopically. If vibrios are present in large numbers they may be detected by their scintillating rotatory movements in hanging-drop preparations, or by their characteristic shape in fæcal films stained by carbolfuchsin. According to Koch, a rough diagnosis may be made in 50 per cent. of cases by this method. If vibrios are very numerous, plates may be spread direct by means of a platinum loop on alkaline agar, or on Dieudonné's medium. When the vibrios are present in small numbers—(*a*) alkaline peptone water should be inoculated with two or three loopfuls of the fluid stool and incubated for seven hours. (*b*) Any pellicle present on the surface of the broth should be examined in stained films or by means of the hanging-drop method. (*c*) If vibrios are scanty, reinforce by inoculation a second alkaline peptone tube, incubating

for a further six to eight hours, and plate out on alkaline agar. (*d*) An emulsion of colonies from the plate or from an agar slope sub-culture should be agglutinated against the specific antiserum in high titre.

An agglutination of over 1 : 1000 with a specially prepared serum is strongly suggestive of the true cholera vibrio, which may then be subjected to special biochemical tests.

The carrying out of the full technique of identification demands a considerable amount of time, and as promptness is the first essential in cholera diagnosis, be it of acute cases or of "carriers," other methods of rapid and more or less accurate diagnosis have been devised. Such a one is Bandi's method, which consists in inoculating the suspected fæces into peptone water containing agglutinating serum of such strength as to clump the cholera bacillus in high dilution. Within as short a period as three hours' incubation, it is said that agglutination visible to the naked eye will be present. This method, when employed in a large number of cases, necessarily consumes a large quantity of immune serum.

A modification of this method has been described by Davies and the Editor in the rapid diagnosis of cholera cases and carriers, with satisfactory results. The advantages of such a rapid method are obvious: positive reports may be obtained on a large number of cases in as short a period as eighteen hours, and as many as 200 stools may be examined by one worker during the course of a morning's work. The following are the stages in the technique:

1. Inoculate a platinum loopful of fæces into peptone water, 1-per-cent. peptone, 1-per-cent. NaCl, made distinctly alkaline to litmus.
2. Incubate for eighteen hours.
3. Place a drop of the resulting growth on the slab of Garrow's agglutinometer (Appendix, p. 1036), together with a drop of 1 : 80 anti-cholera serum. The resulting mixture will give a dilution of cholera serum 1 : 160. On the next partition drop an equal quantity of normal saline, together with a drop of the peptone culture, to act as a control. Rotate for three minutes. If vibrios are present a definite agglutination will be obtained. This can be confirmed later by agglutinating with cholera serum in still higher dilutions. It is recommended that stock bottles (with rubber caps) of cholera serum preserved with 0·5-per-cent. carbolic acid, in dilutions 1 : 80, 1 : 160, 1 : 320, 1 : 640, be kept. If an agglutination is obtained with the lower dilutions it may subsequently be titrated with the higher ones.
4. The peptone culture can then be spread with a platinum loop on Crendiropoulo's agar (alkaline agar), and a pure culture obtained by this means. The cholera colonies can easily be recognized by their transparent bluish-grey appearance. The hæmolytic and sugar tests may then be applied. It has been found that vibrios agglutinating with specific serum in high dilutions invariably give correct sugar, hæmolytic, and cholera-red reactions (p. 479).

In an autopsy on a suspected case of cholera, at least two sections of the small gut, each about 5 in. in length—one just above the ileocæcal valve, the other in the middle of the ileum—should be ligatured, cut off, dropped into sterile saline and sent to a bacteriological laboratory as soon as possible for examination.

An agglutination reaction is not obtainable from the blood-serum

during the acute stage, but it is present after eight to ten days from the commencement of the disease, reaching its maximum in four weeks ; it may attain a titre of 1 : 1000.

Taylor has made it plain that the question of H and O agglutinins is important in the diagnosis of cholera, as it is in other intestinal diseases of bacterial origin. The H element is present in some strains of true cholera and also in all the saprophytic water vibrios. It is affirmed that the O agglutinin is all-important. Evidence is accumulating that the O groups of vibrios are responsible for all serious outbreaks of cholera. Therefore it is important that sera from cholera cases should be tested for O agglutinins.

Differential diagnosis.—True cholera may have to be differentiated from *ptomaine*, or *mushroom* poisoning, which may simulate it very closely, but in this instance there is usually a history of several persons having been attacked at the same time, after having partaken of a particular article of food, especially if it was tinned. It is said that leucocytosis is absent in food-poisoning and is usually found during the early stages of cholera.

As the practical diagnosis of cholera from food poisoning is so important, Tomb has given the useful table on the next page.

Algid or choleraic subtertian malaria may simulate true cholera very closely (*see* p. 81); *acute bacillary dysentery* may occasionally be so sudden and severe in its onset as to resemble cholera ; in *arsenical poisoning* vomiting is more usually the most urgent commencing symptom. Children suffering from cholera are apt to develop hyperpyrexia with cerebral manifestations, which may be diagnosed as meningitis.

Treatment

During cholera epidemics it is customary to establish depots where sedative and astringent remedies for the treatment of diarrhœa are dispensed gratuitously. Chlorodyne in small doses, 10–15 drops, has been found to be of value in staying the progress of the disease.

In the early stages of evacuation opium is of undoubted value. A hypodermic injection of morphia, $\frac{1}{4}$ gr. with atropine gr. $\frac{1}{100}$, should be given immediately. An anti-diarrhœic of proven value is as follows :

℞	Sodi. bicarb.	gr.xv	(0·972 grm.)
	Cret. prep.	gr.xv	(0·972 grm.)
	Spirit. æther.	♏xv	(0·88 c.c.)
	Spirit. ammon. aromat.	♏xv	(0·88 c.c.)
	Tinct. opii	♏xxx	(1·77 c.c.)
	Aq. chlor. ad.	℥i	(28·4 c.c.)

Of this, 1 fl. oz. should be given every twenty minutes till purging and vomiting cease.

Kaolin, or " bolus alba," as an intestinal astringent in large doses adsorbs toxins, thus rendering them inert. It consists of kaolin[1]

[1] Kaolin powder suitable for this purpose may be obtained from the Electric Osmosis Co.

	Cholera.	Food Poisoning.
Diarrhœa.	Painless. Precedes vomiting.	Associated with some intestinal pain. Follows vomiting.
Vomiting.	Causes no distress. Watery and projectile; follows diarrhœa.	Often violent and distressing. Vomit consists of food and is never watery. Copious or projectile. *Generally precedes diarrhœa.*
Nausea.	Absent.	Constant.
Retching.	Rare.	Constant, often severe.
Abdominal pain.	Rare.	Constant.
Tenesmus.	Absent.	Common.
Stools.	Watery and copious.	Liquid, fæcal, and offensive. Never colourless and copious.
Urine.	Complete suppression.	Never suppressed.
Muscular cramps.	Constant and severe.	In very severe cases and confined to extremities.
Collapse.	Frequent. Chiefly from loss of fluid.	Faintness and syncope from toxæmia.
Fever.	Surface temperature below normal.	Axillary temperature 99–102° F.
Headache.	Absent.	Frequent.

200 grm. (7 oz.) in 400 c.c. (14 oz.) of water. This is a single dose, but if there is vomiting it may be repeated, and sipped in small amounts at a time. It is inconvenient to give on a large scale, on account of the bulkiness of the dose.

It has been shown that the adsorption-rate by kaolin is much more rapid in the case of the cholera vibrio than with an emulsion of equal strength of cholera and typhoid, and quick adsorption is one of the reasons why kaolin in massive doses is beneficial in the treatment of cholera.

Subsidiary measures.—The patient should be kept strictly in the horizontal position, in a warm bed, and in a well-ventilated, but not too cold room. His thirst should be treated by sips of iced water or of soda-water, or champagne, or brandy and water. Copious draughts, as they are likely to provoke vomiting, are usually condemned. It does not follow from this that they are harmful; the emesis contributes to the elimination of germ and toxin. Cramps may be relieved by gentle frictions with the hand or with ginger-root, by a small hypodermic injection of morphia, or, these failing, by short chloroform inhalations. The surface of the body should be kept dry by wiping it with warm

dry cloths, and the surface heat maintained by hot-water bottles or warmed bricks placed about the feet, legs, and flanks. The patient must not be allowed to get up to pass his stools ; a warmed bed-pan should be provided for this purpose. The foot of the bed should be raised. All food should be withheld while the disease is active.

Essential oils.—A standard method in India, emphasized by Tomb in the treatment of cholera is by an essential-oils mixture, made up as follows :

℞	Spirit. æther.	♏xxx	(1·176 c.c.)
	Ol. anis.	♏v	(0·296 c.c.)
	Ol. cajup.	♏v	(0·296 c.c.)
	Ol. junip.	♏v	(0·296 c.c.)
	Acid. sulph. aromat.	♏xv	(0·888 c.c.)

Half a drachm (1·176 c.c.) in half an ounce of water, every quarter of an hour. Total dose, 8–14 drachms.

This mixture should be given immediately, when practicable, but it is claimed that in most cases recovery will be secured within a period of seven hours from the onset of symptoms. No special care need be paid to the subsequent dieting of the case. Vomiting, purging, and intestinal pains appear to be immediately controlled by the mixture. The value of the method in the mass treatment of natives is obvious, as little supervision is requisite.

For the stage of collapse which is due to the loss of a large amount of fluid from the system, intravenous injections of salines must be resorted to in order to restore the balance. The collapse in cholera does not differ fundamentally from collapse from hæmorrhage, and similar principles of treatment underlie both. Intravenous injection of salt solution is therefore indicated. Normal saline solution, if given in sufficient quantities acts well. Success appears to depend upon the introduction of a sufficient quantity. Three to four pints may be necessary. Should the veins be difficult to find, transfusion may be performed into the peritoneum or under the breast. After introduction of two to four pints of saline into the peritoneal cavity, the veins soon become prominent and intravenous injection can be carried out.

Rogers's treatment.—Rogers, believing that collapse in cholera was due to excessive loss of chlorides from the blood-stream, introduced a method of treating cholera by intravenous injection of *hypertonic* saline solution. Since the introduction of this method the case-mortality from this disease has been greatly reduced. Owing to collapse of the veins, it is generally necessary to cut down on them in order to insert the cannula. The hypertonic solution is composed as follows : sodium chloride, 120 gr. ; potassium chloride, 6 gr. ; calcium chloride, 4 gr. ; sterilized water, 1 pint. The fluid in the containing bottle should be at a temperature of about 100° F. if the rectal temperature is below 99° F. ; if the latter is above 100° F., as there is risk from hyperpyrexia, the injection should be given at a temperature between 80° and 90° F. This solution is introduced by means of a

special stopcock cannula and transfusion bulb at the rate of not more than 4 oz. a minute, the flow being slowed down to 1 oz. if distress or headache supervenes. From three to six pints should be given, if possible. On an average fifteen minutes should be taken to run in two pints of fluid. At the same time potassium permanganate in solution or in pill by mouth up to 50 gr. a day is given as a means of destroying the toxins formed in the alimentary canal—2 gr. every quarter of an hour for two hours, then every half-hour till the stools are coloured green. These pills are made up in some inert material, such as kaolin and vaseline, without the addition of any oxidizable substance. They are coated with salol, in the proportion of one part of the latter to five parts of sandarach varnish.

With the intravenous saline Rogers combined hypodermic injections of atropine $\frac{1}{100}$ gr., morning and evening. The principles upon which the treatment is provided are as follows:

1. A blood-pressure below 70 mm. of mercury indicates a dangerous collapse, and a specific gravity of the blood of 1063 or over. In the acute stage of the disease the specific gravity of the blood varies between 1060 and 1072, the normal figure for a European adult being 1058 and for an Eastern native 1056.
2. A specific gravity of 1063 indicates a loss of half the fluid from the blood and, for correction, an injection of 3–6 pints.
3. The subsequent fall of blood-pressure to 70 mm. or under, or rise in the specific gravity to 1063, indicates repeated injections morning and evening.

The specific gravity of the blood is estimated by employing a series of small bottles of aqueous glycerin with specific gravities increasing by 2° per bottle from 1048 to 1070. The specific gravity may be controlled by employing a urinometer. Blood from the patient is dropped on to the surface of the fluid in the bottles by means of a capillary pipette. A drop of blood which remains stationary in the centre of the glycerin solution of a given strength indicates its specific gravity.

Previous to the introduction of Rogers's method, Cox of Shanghai had encouraging results from continuous, prolonged, slow intravenous injections of isotonic saline fluid given by a special apparatus placed 2½ ft. above the level of the patient's arm. The flow is kept up for several hours, at a rate of 2 oz. per minute, as long as there is danger from collapse. The saline injections may be combined with 5-per-cent. glucose, which may act beneficially in cases of urinary suppression. De Raymond has had good results with a modification of this method combined with the injection of 5 c.c. of gonacrine daily.

In the stage of collapse, suppression of urine often occurs, and every effort must be maintained to re-establish the blood-pressure. Pituitary extract, or pitressin is often useful during the stage of reaction, given in doses of ½ to 1 c.c., injected hypodermically, two to four times a day; adrenalin may also be given, but its action is more transitory. Caffeine citrate 5 gr. is useful as a cardiac tonic and as a diuretic; it may be given three or four times during the twenty-four hours. Tincture of strophanthus, 5 min., given three times a day may be em-

ployed as an adjuvant. In cases of complete suppression, dry-cupping over the lumbar region morning and evening by means of Fenwick's cups is useful to re-start the flow of urine, and may be supplemented by hot dry fomentations. Rectal injections of hyperalkaline saline—150 gr. of sodium bicarbonate to the pint of isotonic saline—should be administered slowly every 2–4 hours in cases where collapse has been overcome, but suppression of urine persists. Sellards has had success in combating anuria by intravenous injections of 2-per-cent. sodium bicarbonate, and when there is marked acidosis this treatment is indicated. The objection to using sodium bicarbonate is that this salt has a lytic action on the red cells *in vitro*, but when given in 4–5-per-cent. concentration it has no hæmolysing effect upon them. In sterilization the bicarbonate tends to be converted into the carbonate, but Sellards found that by sterilization in an autoclave connected with live steam at 7-lb. pressure, this process was minimized.

During the stage of reaction, should purging persist, large doses of salicylate of bismuth with a little opium may prove of service. If the secretion of urine is not quickly restored, large hot poultices over the loins, dry-cupping of the same region, and the judicious use of bland diluents should be resorted to. Injections of digitalin, $\frac{1}{100}$ gr., may be given to stimulate the cardiac action. Subcutaneous injection of 4–6 mgm. of adrenalin is also recommended. Retention of urine must be inquired about, and the region of the bladder frequently examined, and, if necessary, the catheter employed. In the event of constipation, purgatives must be eschewed and simple enemata alone used.

In cholera convalescents the diet for a time must be of the simplest and most digestible nature—diluted milk, barley-water or rice-water, thin broths, meat juice, and so forth—the return to ordinary food being effected with the greatest circumspection.

Cholera typhoid must be treated much as ordinary enteric fever.

Bacteriophage in the treatment of cholera.—Much has been written in recent years of the treatment of cholera by the specific choleraphage introduced by d'Herelle. Judged by the published returns the results have not been very convincing. Asheshov, Khan, and Lahiri have been giving the bacteriophage together with intravenous hypertonic solution in the same method as already described. Sterilization, however, is done under pressure in the autoclave (30 minutes at 120° C.) and not by boiling. Three pints of hypertonic saline are given intravenously, together with an additional pint of alkaline salt solution (150 gr. sodi. bicarb. to a pint of normal saline). Together with this the cholera bacteriophage is given undiluted by the mouth in one drachm doses every 30 minutes, or 5 c.c. intravenously for more rapid action.

Anticholera serum.—Ghosh and others have tried the effects of injection of a new anticholera serum of an increased potency. This has been produced by a modification of toxin production with the object of obtaining a maximum quantity of both endo- and exotoxin. The serum is best injected intraperitoneally in doses of 70–80 c.c. The results are stated to be encouraging,

and it was found that in cases with a blood specific gravity of 1064 or more, the mortality was reduced by more than 50 per cent. No cases of uræmia occurred in the series. The intravenous injection of the serum is by no means so favourable as the intraperitoneal.

Mortality-rate.—Tomb has given a statistical table of the mortality rates in a series of 2,826 cases during a period of six years, 1922-1928.

Methods of Treatment	*Death-rate*
Untreated (112 cases)	91·0 per cent.
Essential-oil mixtures	26·5 ,,
Saline injections	47·1 ,,
Cholera mixtures	52·9 ,,

Prophylaxis. *Quarantine prevention.*—Theoretically, quarantine should be an efficient protection against the introduction of cholera into a community; practically, it has proved a failure. Unless they are stringent and thoroughly carried out, quarantine regulations can be of little use. Even if the utmost care, intelligence, and honesty succeed in excluding individuals actually suffering from cholera, or likely within a reasonable time to suffer from cholera, there is yet no guarantee that the germ of the disease may not be introduced. Convalescent patients may pass vibrios in their stools for as long as forty-four days. It was estimated that in the Naples epidemic of 1911, 90 per cent. of the cases were due to direct contact with patients or with healthy carriers; while in the Colombo outbreak in 1926, of 442 contacts examined, 10 per cent. were found to be carriers of *V. choleræ*. For the recognition of the carrier state it is necessary, following the technique given at p. 485, to examine the stools of all contacts for the vibrio. A small dose of calomel to clear out the contents of the small intestine greatly increases the chance of recovering the specific organism from stools. This is the only scientific method of conducting a reliable quarantine.

The system to which Great Britain apparently owed her immunity during epidemics on the continent of Europe is a practicable and, in civilized conditions, an efficient one. Under this system, only ships which were carrying or which had recently carried cholera patients were detained; and even these merely till they could be thoroughly disinfected. Thus inconvenience and loss to travellers and merchants were small, and the temptation to conceal cases of the disease or to evade regulations was proportionately minimized. Any cholera cases were isolated in suitable hospitals, the rest of the crew and passengers, although supervised for a time, being given free pratique. At the same time attention was not diverted from the sanitation of towns, especially of seaports—the measure mainly relied upon. Suspicious cases occurring on shore were at once reported to the sanitary authorities and promptly dealt with, fomites being destroyed or disinfected at as little cost and inconvenience to individuals as possible. Every

endeavour was made to prevent fæcal contamination of the public water supply.

Of late years, in India, preventive measures have been conducted much on the same lines, attention being given to sanitation rather than to quarantine. During the great religious festivals the sanitary condition of the devotees is looked after as far as practicable, special care being given to provide them with good drinking and bathing water.

Among the troops in India, on the appearance of cholera in their neighbourhood, special protective measures are promptly instituted, elaborate directions having been drawn up for the guidance of medical officers.

Wells and water supplies during a cholera epidemic should be treated with potassium permanganate till the water becomes pink; an appropriate strength is 60 gr. to the gallon of water. The water should be left till colourless for twenty-four hours, and all vegetation and aquatic fauna removed.

The application of bacteriophagic principles to sanitation.—According to Graham and Morison, choleraphage is absent in the intestinal tract before the start of a cholera epidemic. Little or no phage is found in the first victims to be stricken, and this factor is elaborated as the epidemic progresses, so that those patients who develop a rapid exaltation of choleraphage recover, so that this substance can be used as a prophylactic measure in disinfecting wells. For this purpose 30 c.c. of potent bacteriophage were added to two wells in the contaminated area. One case only subsequently developed in those who drank this water.

The essential-oils mixture (p. 489), if administered in doses of 1 drachm in ½ oz. of water daily, appears to be a good preventive. Its probable value is indicated by the fact that, under its influence, house infection (i.e. infection of other members of the household) appears to be obviated.

Incubation period.—All quarantine and protective systems must take cognizance of the fact that, although cholera may declare itself within a few hours of exposure to infection, it may also do so at any time up to ten days thereafter; three to six days may be set down as the usual duration of the incubation period.

Haffkine's inoculation.—During the Great War many millions of anticholeraic inoculations were made. The initial dose is ½ c.c. of an emulsion of 4,000 millions, followed seven to ten days later by a second inoculation of 1 c.c. containing 8,000 millions. Experience has shown that even larger doses can easily be tolerated. The local reaction is, generally speaking, a very mild one. There may be œdema and a painful infiltration at the site of the injection, rarely followed by systemic disturbance.

Several strains of cholera vibrios are used. They are inoculated into Roux bottles containing "pea-extract agar" and grown for forty-eight hours. The growth is washed off with normal saline, and the emulsion counted, dark

ground illumination being employed. The emulsion is then heated to 55° C. for one hour, after which 1-per-cent. carbolic is added. The emulsion thus sterilized is finally diluted down so as to contain 8,000 million vibrios per c.c. of saline and 0·5-per-cent. carbolic.

The immunity thus produced does not seem to be a very persistent one, lasting at the maximum for three or four months.

Subsequent experience, particularly that obtained during the Balkan War of 1913, in Batavia in 1915 and 1916, and in the Great War, has gone far to confirm the earlier impressions of the value of Haffkine's inoculation.

In India from 1905–1916 the annual number of deaths attributed to cholera was never less than 300,000. Epidemics of cholera are readily controlled by the use of vaccine when inoculation is made compulsory; thus when this disease was introduced into Korea from China in 1926 the outbreak was promptly brought to a close by the inoculation of more than one million persons.

Immunization per os.—On the proposition enunciated by Besredka, vaccination by the mouth is now being practised in Russia, where the immunization of large numbers of people is necessary. It is premature to say whether this method is more effective than that outlined above. The vaccine is made from thick suspensions of the organisms killed by heat, carbolic acid, or alcohol, and given in from 3 to 5 doses ranging up to 100 c.c. every other day. Each dose consists of 10–100 milliards of vibrios, or 0·01–0·1 grm. of the dried organisms. The full course of bili-vaccine, as it is called, confers the same degree of immunity as ordinary vaccine, but the immunity produced by a simple inoculation is probably as high as that given by a full course of bili-vaccine. Vickers (1928) has made comparison of the two methods:

I. *Cholera vaccine.*—One dose to 17,160 individuals. Percentage attacked 0·34. Mortality of those attacked, 37·3. Cholera vaccine, two doses, 8,485 individuals. Percentage attacked, 0·37. Mortality of those attacked, 37·6. The number of cases among the unvaccinated was 4·5 times as large as among the vaccinated; the percentage mortality 5·8 times as great.

II. *Besredka's vaccine orally.*—Full course of 3 doses (200,000 million organisms) given to 4,982 individuals. Percentage attacked was 1·36. The mortality of those attacked 22·2 per cent. Of 11,004 untreated individuals 2.02 per cent. were attacked, with a case-mortality of 41·9. The number of cases occurring among the unprotected was 5·6 times the protected and the percentage mortality was nearly double. Russell has made comparative tests of anti-cholera vaccine and the oral bili-vaccine. One objection to the latter in the height of a cholera epidemic is that it gives rise to an acute diarrhœa.

Personal prophylaxis.—During cholera epidemics great care should be exercised to preserve the general health; at the same time, anything like panic or apprehension must be sedulously discouraged. Fatigue, chill, and excess—particularly dietetic or alcoholic—are to be carefully avoided. Visits to cholera districts should be postponed if possible, seeing that the newcomer is especially liable to contract the disease. Unripe fruit, over-ripe

fruit, shell-fish, food in a state of decomposition, and everything tending to upset the digestive organs and to cause intestinal catarrh, are dangerous. Melons, cucumbers, and the like deserve the evil reputation they have acquired. Purgatives—particularly saline purgatives—unless very specially indicated, should never be taken at these times. All drinking-water, and all water in which dishes and everything used in the preparation and serving of food are washed, should be boiled. Mere chlorination of the water with bleaching powder ($CaOCl_2$), giving 1·3 parts of chlorine per million, or added to water in the proportion of 2 grm. of the powder to every 110 gallons, is not entirely reliable. Sodium bisulphate tablets (2 grm. to 1¾ pints of water), by liberating sulphuric acid, provide a most useful method of sterilizing water for personal use, as for instance in a water-bottle. Filters—except perhaps the Pasteur-Chamberland filter—are not for the most part to be relied upon; in many instances they are more likely to contaminate the water passed through them than to purify it. A good plan in a household or in public institutions is to provide for drinking purposes an abundant supply of weak tea or lemon decoction, the supply being renewed daily; such a plan ensures that the water used in the preparation of the drink has been boiled. All food should be protected from flies. Diarrhœa occurring during cholera epidemics should be vigorously treated.

CHAPTER XXVIII

THE DYSENTERIES AND LIVER ABSCESS

THREE types of dysentery, correlated to three quite distinct and, zoologically speaking, widely separated parasites are now definitely established. Though of a totally different ætiology they are not mutually exclusive, for one type may be superimposed upon and complicate another; moreover, any or all of them may complicate some general disease, such as malaria or typhoid. The term "dysentery" is merely a designation embracing a symptom-complex, but not indicating some particular disease of distinct ætiology. It is most important that a sane and critical view should be taken on the all-important matter of differential diagnosis of the dysenteries. There are many large pathological conditions of the intestine which may give rise to a discharge of blood and mucus, but which are not connected with any particular parasitic infection, and these will be dealt with in a section devoted to that subject.

The principal forms of dysentery and their respective parasites are as follows:

I. BACTERIAL—
- THE BACILLARY DYSENTERIES:
  - *Bacterium dysenteriæ*—Shiga, Flexner and Sonne.

II. PROTOZOAL—
- AMŒBIASIS—Amœbic dysentery, Liver abscess, etc.
  - *Entamœba histolytica.*
- BALANTIDIAL DYSENTERY:
  - *Balantidium coli.*

III. HELMINTHIC—
- BILHARZIAL DYSENTERY:
  - *Bilharzia mansoni*, *B. hæmatobia*, or *B. japonica.*
- VERMINOUS DYSENTERY:
  - *Œsophagostomum apiostomum*, or *Œ. stephanostomum.*

I. BACILLARY OR EPIDEMIC DYSENTERIES

Definition.—An acute epidemic disease due to invasion of the mucosa of the large intestine by a specific bacillus (*B. dysenteriæ* Shiga, Flexner, or Sonne's bacillus). Pyrexia, symptoms of toxic absorption, and the discharge of blood-stained mucus in the stool usually occur. In severe cases coagulation necrosis of the mucosa

may take place and quickly lead to death. In the milder forms the clinical symptoms may be those of a simple diarrhœa.

Geographical distribution.—Epidemics of bacillary dysentery are of frequent occurrence, both in the tropics and in temperate countries. At the present day such epidemics are of greater intensity and frequency in those countries in which the insanitary habits of the natives and more primitive conditions of life lend themselves to the spread of disease. In mediæval times it would seem that bacillary dysentery epidemics were much more widespread and virulent at a time when the sanitary conditions were more akin to those found among primitive tropical natives at the present day. In Europe, bacillary dysentery is to-day mainly an institutional disease, occurring not infrequently as outbreaks in lunatic asylums, prison camps, and military barracks. In the Gallipoli campaign this disease was responsible for the majority of the 120,000 medical casualties evacuated from the Peninsula within three months.

Epidemiology.—In the tropics and subtropics, bacillary dysentery appears to observe a definite seasonal incidence. It is certainly prevalent during the rainy season and for a short period subsequent to this, but is most prevalent in the autumn months, while minor epidemics may occur in the early spring months as well. During the hot dry African summer the disease appears to be in abeyance.

Its spread from man to man takes place, either by direct or by indirect contagion.

Bacillary dysentery has always been a scourge of war. If we may trust the records of history it was an important factor in the Napoleonic wars, in the Franco-Prussian War of 1871, and in the South African War of 1900-1902. Large epidemics of bacillary dysentery occurred in all belligerents during the Great War, and as a cause of invaliding was hardly secondary to that of any other disease. In the Middle East, India, Mesopotamia and East Africa the general tendency was to mistake, for reasons pointed out on p. 511, amœbic for bacillary dysentery. That bacillary dysentery was the predominating form in every epidemic of war dysentery from the Gallipoli campaign onwards was pointed out by the Editor and others in 1915.

Direct contagion by fæces can occur, as a rule, only among primitive communities in which the ordinary sanitary observances are either unknown or disregarded. Its occurrence and spread in lunatic asylums and Indian bazaars are attributable to personal habits which lend themselves to the spread of infection.

Indirect contagion. (*a*) *Flies.*—There appears to be little doubt that houseflies (*Musca domestica*) act as carriers of the infection. The seasonal incidence of bacillary dysentery corresponds in a remarkable manner with the maximum prevalence of these pests.

In 1910 the Editor demonstrated dysentery bacilli, in considerable numbers, in the intestinal tract of houseflies taken in an endemic area, and this work has since been confirmed by Taylor and others.

The housefly is able to spread dysenteric infection in two ways—firstly, by its habit of regurgitation preparatory to feeding on food for human consumption; and secondly, by its fæces. The latter is probably the more common. Buxton has found that the intestinal canal of the majority of houseflies caught in Iraq contained human fæces. One can therefore understand the importance of the insect in the spread of this disease, as it is strongly attracted by dysenteric fæces.

(*b*) *Water* acts as a medium of infection, especially in the Malay States (Fletcher and Jepps). It has been shown that the bacillus can survive in drinking-water for over three weeks, but not for so long a period if exposed to the sun or when associated with numbers of putrefactive micro-organisms.

(*c*) *Milk*.—Several outbreaks of Flexner dysentery in south England and on the Continent have been ascribed to the contamination of milk, but the evidence has not always been very convincing. In the case of Sonne dysentery this method of conveyance has been definitely proved by Bowes (1938).

(*d*) *Food*.—Sonne dysentery is very definitely a food infection, and can be classified among the group of food-poisonings. One of the best authenticated outbreaks was described in London in 1933, and was due to eating "pease pudding."

(*e*) *Susceptibility of the individual*.—New arrivals in the tropics are specially liable to contract this form of dysentery, and small children are susceptible. Patients whose resistance has been undermined by any other intercurrent disease, such as malaria, pellagra, and tuberculosis are apt to contract a terminal dysentery.

(*f*) *Carriers* (*see* p. 509).

Ætiology.—*B. dysenteriæ* was discovered by Shiga in 1898, and confirmed two years later by Kruse in Germany. It is also known as the Shiga-Kruse bacillus.

Shiga's bacillus is a rod-shaped Gram-negative organism, 1 to 3 μ in length by 0·4 μ in breadth; it is non-motile, and often exhibits very active Brownian movement. Vedder and Duval have demonstrated numerous lateral flagella of great tenuity; no spore-formation occurs. On agar and gelatin it grows as a thin smooth film with regular margins, and on agar and MacConkey plates its colonies much resemble those of the typhoid bacillus; they are regularly round, light-blue in colour, and dew-like. It produces no liquefaction of gelatin, and grows as a transparent, almost invisible, layer on potato. After a brief preliminary acid-production in milk, it gives rise to a gradually increasing alkalinity. With solutions of the various sugars (*see* Table on p. 499) it produces acidity in glucose, but is inert in this respect in the rest of the series; it does not produce indol in peptone water. It is agglutinated in high dilutions by the serums of patients suffering from the disease. It occurs in considerable numbers in dysenteric lesions, and in the mucous stools of the corresponding period of the disease.

Varieties of Shiga's bacillus (resembling that organism in its sugar reactions, *but forming indol* and not agglutinating with Shiga-immune serum) have been described during recent years, but it is doubtful whether they

TABLE XXI.—BIOLOGICAL REACTIONS OF PATHOGENIC AND ALLIED ORGANISMS RECOVERED FROM THE FÆCES.

	Mannite		Glucose		Maltose		Lactose		Saccharose		Dulcite		Litmus or Phenol Red Milk			Indole	Motility
	A	G	A	G	A	G	A	G	A	G	A	G	A	Alk	Clot		
Bact. shigae	0	0	+	0	0	0	0	0	0	0	0	0	+	0	0	0	0
Bact. flexner	+	0	+	0	+	0	0	0	0	0	0	0	+	+	0	+	0
Schmitz's bacillus	0	0	+	0	0	0	0	0	0	0	0	0	+ sl	0	0	+	0
Sonne's bacillus	+	0	+	0	0	0	+	0	+ or 0	0	0	0	+	0	+	0	0
Bact. dispar	+	0	+	0	0	0	+	0	0	0	±	0	+	0	+	±	0
Bact. morgani	0	0	+	+ sl	0	0	0	0	0	0	0	0	0	+	0	+	+
Bact. typhosum	+	0	+	0	+	0	0	0	0	0	0	0	+	0	0	0	+
Bact. paratyphosum A	+	+	+	+	+	+	0	0	0	0	+	+	+	0	0	0	+
* *Bact. paratyphosum B.*	+	+	+	+	+	+	0	0	0	0	+	+	+	+	0	0	+
* *Bact. enteritidis*	+	+	+	+	+	+	0	0	0	0	+	+	+ sl	+	0	0	+
Bact. coli	+	+	+	+	+	+	+	+	0	0	+	+	+	0	+	+	+
Bact. fæcalis alkaligenes	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	+
Bact. acidi lactici (Hüppe)	+	+	+	+	+	+	+	+	0	0	0	0	+	0	+	+	0

A = acid, G = gas, Alk = alkaline, Sl = slight.

* To differentiate *Bact. enteritidis* and other organisms of the food-poisoning group from *Bact. paratyphosum B.* serological tests must be applied.

are of ætiological importance. They may possibly be secondary infections. Several species, that of Schmitz, of d'Herelle, the *B. ambiguus* of Andrewes, the para-Shiga +, or —, of Dudgeon, fall into this category.

Cultures of Shiga's bacillus are extremely toxic to laboratory animals, especially the rabbit. But in these animals they do not produce lesions characteristic of dysentery, though the filtered toxins, when injected intravenously, cause necrosis of the large intestine, on which they appear to exert some selective action. In two experiments in man, one intentional, the other accidental, ingestion of pure cultures was followed, within a short time, by well-marked symptoms of dysentery.

The causal relationship of the bacillus to disease is practically established.

Flexner's bacillus (the Flexner group).- In 1900 an organism morphologically similar to Shiga's bacillus, but differing in the production of acid from mannite as well as glucose, producing indol from peptone somewhat irregularly, and inagglutinable with Shiga-immune serums, was isolated by Flexner from cases of dysentery in Manila. Since that date a very large number of organisms belonging to this group have been described. Among the number may be cited the bacillus of Strong and the Y bacillus of Hiss and Russell, both of which were thought at first to differ in their biochemical and serological reactions, but this is now known not to be the case. From the work of Andrewes and Inman on a very large number of strains of the Flexner—*a mannite-fermenting group* it can be definitely stated that the organism does not adhere to one constant type, as does Shiga's bacillus, but differs greatly in the toxicity of the various strains and in their antigenic properties. A basis for satisfactory sub-grouping is the serological method of Murray, Andrewes, and Inman. From their work it appeared that five definite strains of the bacillus can be identified, known respectively as V, W, X, Y, Z, and for their recognition five specially prepared homologous serums are necessary. A pooled preparation of these five components is now obtainable for laboratory purposes and may be employed for the recognition of the bacillus, but a more recent study (Boyd, 1938) of antigenic variation among mannite-fermenting dysentery bacilli finds the loss in culture of *type-specific* antigen, which is not shared by other members of the group, and is associated with an increase, real or apparent, of non-specific *group* antigen. A different explanation of the observations of Andrewes and Inman detailed above is thus put forward. It seems probable that available cultures of the historical Hiss and Russell Y are degenerate variants of an original W strain, and that an Indian strain, 103A, is actually the type-specific Flexner-Y. This strain has been found to be fairly common, both in the United Kingdom and in other parts of the world (W. M. Scott, quoted by Boyd). This study emphasizes the great importance of using type-specific suspensions in diagnostic agglutination tests. Stock Flexner-Y strains may on these grounds be almost or quite devoid of type-specific antigen.

Sonne's bacillus (*Bacterium dysenteriæ Sonnei*), an organism of this group, but which ferments lactose slowly, is responsible for outbreaks of enterocolitis in Egypt and elsewhere (Perry), and may produce symptoms of food poisoning resembling those of the *Salmonella* group. The importance of this infection has been recognized in England and in America during recent years as a

cause of dysentery and diarrhœa of definite seasonal occurrence, especially in children. The colonies of this bacillus tend to assume a much more crenated outline than do those of the Flexner type, but are usually larger than those of Shiga or Flexner or MacConkey's medium. Cultures of Sonne's bacillus are not agglutinated by standard Flexner or Shiga sera. When titrated against a specially prepared Sonne anti-serum, agglutination to full titre occurs. Often, however, when freshly isolated it is inagglutinable, but will remove the agglutinins from Sonne serum by absorption. On MacConkey's medium, Sonne colonies frequently show a small central point of acidity on a somewhat opaque background. Sonne's bacillus is indol-negative and zylose-negative. It ferments glucose and mannite in twenty-four hours, and lactose and saccharose after some days. Serological varieties and strains are now recognized. Though not so toxic as Shiga's bacillus, Sonne's bacillus, when injected into rabbits, may produce sudden death.

As a general rule, dysentery bacilli can be isolated only from the intestinal canal and the mesenteric glands. The organisms have also rarely been obtained from the blood-stream, gall-bladder and joint-effusions.

Apparently both the Shiga and Flexner bacilli are encountered in sporadic cases and in some epidemics without a preponderance of any one particular type; but it may be said that Shiga's bacillus is of more frequent occurrence in the tropics than in temperate zones, and is responsible for the most severe clinical forms of the disease, and consequently for the most virulent epidemics.

Pathology.—The primary lesions of bacillary dysentery (Shiga and Flexner infections) are confined to the solitary follicles of the large intestine, and result in a sinuous "snail-track" ulceration of the folds of mucous membrane. In very acute cases the process consists of intense hyperæmia of the large intestine, which eventually culminates in gangrene of the mucosa of the entire colon, as well as of the last 2–3 ft. of the ileum. Exceptionally the whole of the mucosa of the small intestine may be involved.

As a general rule, the lesions characteristic of bacillary dysentery are most pronounced in the lower part of the intestinal canal, from the sigmoid flexure to the anal canal. In the stage of *necrosis* the large gut is contracted so as to resemble a rigid tube, and the mucous membrane is converted into a rigid, resistant, olive-green or blackish substance (Plate XIII, Fig. 3). Its colour is thought to be due to the staining of the necrotic tissue by bile-pigments. Occasionally this necrosis may have a patchy distribution affecting especially the descending and pelvic portions. There are many signs of an acute toxæmia.

When the necrotic patches have a more local distribution, irregular ulcers, often communicating with one another by submucous sinuses, form and may involve the entire wall; such a bowel surface has a fenestrated appearance.

Chronic ulceration of the large gut may occur in bacillary dysentery. The smallest lesions are lenticular in shape and involve the mucous surface alone. The more advanced lesions amount to ulceration of limited tracts of mucous membrane, rarely penetrating below the muscularis mucosæ. Ante-mortem perforation of the gut may supervene, though it is extremely

rare. For the differentiation of these ulcers from those of amœbic dysentery the reader is referred to the Table on p. 513.

These ulcers must also be distinguished from those of tuberculous, enteric, or bilharzial origin, and also of ulcerative colitis. In some chronic cases the mucous membrane may be entirely destroyed, rendering recovery impossible. The gut then resembles a piece of chamois-leather with interlacing fibrotic strands on the surface.

Mucous retention cysts, due to the formation of pseudo-adenomata from the bases of Lieberkühn's follicles, may sometimes be found as a sequela of bacillary ulceration, and were first described by the Editor. They may be recognized as jelly-like elevations forcing up the mucous surface and scattered throughout the length of the large gut. Dysentery bacilli may be isolated from their contents, and they are probably present in the large intestine of "carriers" of the disease (Fletcher and Jepps).

Formation of granulation tissue.—Many cases of chronic bacillary dysentery acquired in the Great War showed no ulceration, but only a granular condition of the mucous membrane of the large gut. The lesions are distributed, as a rule, in an irregular manner; more usually confined to the lower portion of the large intestine. Considerable infiltration of the walls of the gut is associated with this condition. As in ulcerative colitis, stenosis of the large intestine, either localized or general, may take place as the result of this disease. Mixed infection of amœbic and bacillary dysentery may be sometimes met with.

Histopathology.—The submucosa is the seat of numerous hæmorrhages and of round-cell infiltration (Fig. 57). The formation of macrophage cells from the capillary endothelium of the vessels may also be observed. Owing to their large size, hyaline appearance, and vacuolated protoplasm, these cells, even in microscopic sections, are liable to be mistaken for *Entamœba histolytica* (Plate XIV).

The pathological appearances of Sonne dysentery are not so well known as are those of Shiga and Flexner infections. From a study of available material, it can be stated that the changes are similar, but not by any means so severe (Plate XIII, Fig. 2).

Symptoms.—After a short incubation period, usually of from one to seven days, as ascertained by experiment, the disease begins in a variety of ways, suddenly or insidiously, in all degrees of severity, varying from a mild diarrhœa to an acute fulminating choleraic attack.

The main clinical symptoms are those of inflammation of the large intestine, viz., griping, tenesmus, the frequent passage of loose, scanty, muco-sanguineous stools, often with dysuria.

The onset may be attended with high or moderate fever, or there may be no material rise of temperature. The symptoms may be grafted on to some general disease such as scurvy or malaria, or on to some chronic disease of the alimentary canal, as sprue; they may assume acute characters, or from the outset they may be subdued in degree. As a general rule, the nearer to the rectum the lesions the more urgent the tenesmus; the nearer to the cæcum the more urgent the griping. The general constitutional symptoms due to the absorption of toxins may be very marked. Vomiting may occur from the outset or be absent altogether.

Palpation of the abdomen can be effected only with difficulty during

the early stages, owing to the protective rigidity of the recti muscles. Later, especially in toxic and fatal cases, the abdomen may become quite lax and the spastic and contracted sigmoid colon can easily be distinguished, as an elastic cord, under the examining hand. The

Fig. 57.—Microscopical section of large intestine in bacillary dysentery, showing necrosis of mucosa, cellular infiltration, and hæmorrhages into submucosa.

implication of other portions of the large intestine can seldom be satisfactorily detected by a physical examination.

Character of the stools.—At first fæcal and diarrhœic, the evacuations may vary enormously in number and character in the different types. Their number may be uncountable, the unfortunate victim being " glued to the commode." When they acquire definite

characters, they consist of extremely viscid blood-stained mucus, which has been compared to " red-currant jelly " or " frog's spawn," and are generally odourless. The characters by which the exudation may be distinguished from the amœbic stool are given on p. 514. A few teaspoonfuls only may be passed at a time ; subsequently the stools contain less blood and assume a more purulent character. Finally, the biliary pigments make their appearance, and the fæcal character of the stool may reappear.

In the most acute and fulminating forms the mucus may contain a large proportion of dark blood and resemble " meat washings." When necrosis of the mucosa has become finally established the stools may be exceedingly offensive, grey in colour, and contain much altered blood but no mucus.

On clinical grounds, bacillary dysentery may be classified under various headings, as follows :

1. *Mild or catarrhal forms.*—A common history is that for some days the patient had suffered from what was supposed to be an attack of diarrhœa. The stools, at first bilious and watery, perhaps to the number of four or five in the twenty-four hours, had latterly and by degrees become less copious and more frequent, less fæculent and more mucoid, their passage being attended by a certain amount of straining and griping.

At the same time the tongue may remain clean, and there may be no accompanying pyrexia. The whole attack may be over in a week, and the stools may not number more than twelve in the twenty-four hours. The majority of these mild cases are due to Flexner's or Sonne's bacillus.

2. *Acute bacillary dysentery.*—In another type of case the onset is much more abrupt. Within a few hours of its commencement the disease may be in full swing. The stools, at first fæculent, soon consist of little save blood-stained mucus. Very shortly the desire to stool becomes increased, the griping and tenesmus being accompanied, perhaps, by most distressing dysuria. Fever, which at the outset may have been smart and preceded by rigor, subsides. The face is anxious and pinched, the cheeks are high-coloured from a toxic flush. Slight delirium and mental confusion may be added to the clinical picture. Thirst may be considerable, anorexia complete, and the tongue white or yellow-coated. In a week or more the urgency of the symptoms may diminish, and the attack tapers off into a subacute or chronic condition, or it may end as abruptly as it began (Chart 21).

3. *Fulminating bacillary dysentery.*—The attack generally begins suddenly, it may be in the middle of the night, with chills or smart rigor, vomiting, headache, and a rapid rise of temperature to 100° or even 104° F. Very shortly after the rigor, purging begins, the stools rapidly assuming dysenteric characters. In from two to three days up to a week or longer, collapse sets in with a subnormal tem-

perature, and the patient dies. So virulent may be the toxæmia that death may take place before dysenteric stools are emitted. The tongue is thickly coated, and all the other symptoms of an acute toxæmia are present. The abdomen is sunken and acutely tender. The stools rapidly assume a liquid, offensive character, and are of a greenish or greyish hue. Towards the end neither blood nor mucus may be visible in the stools, whilst in number they may be uncountable.

A *choleraic* form, in many respects resembling cholera, has been noted; these cases are by no means frequent. The onset is acute, with vomiting. Collapse with its attendant phenomena sets in early, and the stools may consist of a watery substance alternating with liquid blood-stained mucus or, it may be, almost pure serum. The temperature is subnormal, and death takes place within three days.

4. *Relapsing bacillary dysentery.*—In a proportion of bacillary dysenteries, although the urgency of the initial attack may subside, symptoms do not completely disappear. The stools may recover

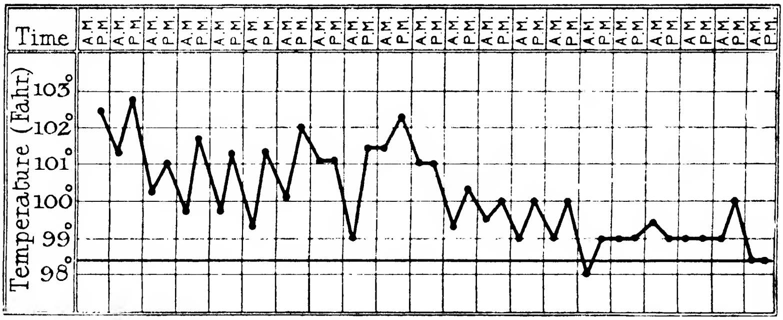


Chart 21. —Bacillary dysentery. (*Orig.*)

their fæculent character, or may even show some signs of formation, yet they continue to be passed too frequently, are often preceded by griping, and contain a variable amount of muco-pus with or without blood. Bacillary cases of this type may be due to a fresh infection, or to a lighting up or recrudescence of an old focus.

5. *Chronic bacillary dysentery.*—In quite a large proportion of cases of acute dysentery the fæces do not become absolutely normal for a considerable time after the abatement of the more urgent symptoms. On the slightest indiscretion, either of food or of drink, the old symptoms reappear. In such cases sudden attacks of diarrhœa are common. For months, or even years, some patients never pass a perfectly healthy stool, the uniform motion always containing slime or muco-pus and at times blood. Often there is a tendency to scybalous stools, or to constipation alternating with diarrhœa. The clinical appearance of these cases is almost characteristic, and this state was formerly known in India as the *Morbus bengalensis*.

Since the end of the Great War a form of chronic bacillary dysentery has been recognized which differs materially from any previously described. As a general rule, the initial attack may have been so mild that it has passed unnoticed, but recurrence of symptoms take place, with passage of blood and mucus, becoming more frequent and severe year by year. Eventually the stool consists of little else than large quantities of blood-stained mucus and necrotic epithelium. The course of these cases is invariably progressive, and, unless vigorously treated, they terminate fatally. Emaciation may be extreme, especially in native races ; an adult man may weigh less than 49 lb. (Fletcher and Jepps). Considerable anæmia may develop, with cardiac failure and dropsy. Death may ensue from exhaustion, or from some intercurrent disease, such as phthisis or malaria.

Bacillary dysentery in children.—Infection with the dysentery bacilli in small children, especially European children, may produce the most acute and rapidly fatal symptoms. The child may die in convulsions before the intestinal symptoms have had time to develop. The cases may resemble meningismus, and often at the onset, on account of the pyrexia and toxic appearance of the patients, infections with the enteric group.

Post-dysenteric ascites.—Megaw is of the opinion that the ascites which is so common in most hospitals in India is a sequel to bacillary dysentery. When bacillary dysentery is not treated, or is improperly handled, the dysenteric toxins pass through the intestinal wall and set up an irritative peritonitis which is followed by fibrosis of the peritoneum. The result is an accumulation of ascitic fluid which is said not to be associated with cirrhosis of the liver ; but the Editor has observed severe interlobular cirrhosis due to absorption from chronic ulceration of the large intestine.

Symptoms of Sonne dysentery.—In most cases mild attacks of dysenteriform diarrhœa are the rule. It is generally stated that the fæces are greenish in colour, with blood-flecked mucus from which the organism may be obtained. In the more acute form, the symptoms more closely resemble those of Flexner dysentery, with sudden onset of colic, diarrhœa, and, later, blood and mucus in the fæces. Sometimes, however, they are more acute still, with pyrexia and vomiting, and they may assume an alarming aspect reminiscent of salmonella infections. In this form, " tomato soup " stools are passed, followed by rapid prostration. In Sonne infections, there is a tendency to pyrexia associated with the abrupt onset, but in the milder cases the fever is slight and transient and the whole clinical picture more resembles food poisoning. A remarkable feature is the association of catarrh of the respiratory tract with diarrhœa, and the catarrh may antecede the development of abdominal symptoms. Very acute Sonne infections in children up to nine years of age may be the cause of sudden death. Some observers believe that in this instance the symptoms are produced, not so much by the actual organisms, as by their toxins in contaminated

food, which forms a medium for their propagation. It appears that Sonne infections are specially liable to attack the insane in mental institutions.

Predisposing causes.—Bacillary dysentery is especially apt to attack those who are in an enfeebled state of health owing to starvation, unsuitable dietary, physical exhaustion, or exposure, or whose health has been undermined and resistance lowered by some chronic disease such as malaria, tuberculosis, scurvy, or enteric. In the feeble-minded, in very young children, in the aged, and in pregnant women, bacillary dysentery is apt to assume a serious and toxic form. Young children may show pronounced symptoms of toxæmia, and die in convulsions or in coma.

Complications.—*Dysenteric arthritis*, or *dysenteric rheumatism*, as it has been called, has long been known to Indian practitioners. An effusion into the cavity and ligaments surrounding the joints, especially the knee and ankle, may come on during the acute stage of the disease, or, as is more generally the case, during convalescence when the stools are more or less fæculent (Fig. 58). It is common in some epidemics, in others it is absent. It is most frequent in Shiga infections. A considerable pyrexia accompanies the joint-effusions. The condition may last a considerable time, but usually clears up without leaving any permanent deformity, though, exceptionally, permanent disability may result. According to G. Graham, complete recovery may eventually ensue, even after it has persisted for six months. The fluid from the joints is sterile,[1] and will agglutinate the dysentery bacillus (Klein) in a titre considerably higher than that given by the blood-serum from the same case. This condition has to be distinguished from fugitive serum-arthritis, such as often occurs after the injection of anti-dysenteric serum, and also from acute rheumatoid arthritis.

Eye complications, etc.—Both acute *conjunctivitis* and *iridocyclitis* are now regarded as symptomatic of dysenteric toxæmia. The former is frequently noted as a complication in association with arthritis, whilst iritis occurs only in a small percentage of cases. The pupils are irregular in outline with ring synechiæ. There is also anterior uveitis, with adhesions to the capsule of the lens formed by a thin membranous film of exudate occupying the pupillary space, causing photophobia, blepharospasm, and marked circumcorneal hyperæmia. The aqueous humour has been found to agglutinate Shiga's bacillus, but the tears do not contain the specific agglutinins. Parotitis, either unilateral or bilateral, has been observed, and is possibly due to septic absorption from the mouth. Intussusception of the large, or of the small, intestine has been found in children, and is in them a common terminal event in acute cases.

That the eye and joint complications referred to are due to an endotoxin is indicated by experimental work on animals. This shows that the filtrates of Shiga cultures, when injected intravenously, lead

[1] Shiga's bacillus has been isolated from the fluid in one instance (Elworthy).

to the production of iritis and arthritis, as well as of local lesions in the cæcum.

Sequelæ.—Stenosis of the large intestine may be the result of an acute attack; pain and abdominal discomfort indicate abdominal adhesions which are an occasional sequel. *Per contra,* the Editor has seen two cases of idiopathic dilatation of the colon which ensued

Fig. 58.—Arthritis of hands and knees in bacillary dysentery.
(*Photo: Dr. G. Hall.*)

as a legacy of the infection. A mucous colitis frequently persists for years. *Peripheral neuritis* may follow bacillary dysentery. The legs are usually affected with the familiar signs of a neuritis. *Post-dysenteric tachycardia*, probably owing to a toxic myocarditis, a condition of irritable heart, persists long after dysenteric symptoms have disappeared. *Achlorhydria*, either complete or a low hydrochloric-acid curve, has been found to be the result of bacillary dysentery, and this

factor has been held to be responsible for many of the digestive troubles which follow in its train.

Bacillus coli infections.—That bacillus coli infections of the urinary tract frequently follow in the train of chronic bacillary dysentery was pointed out by the Editor and Enright (*see* p. 345) and this may to some extent account for the frequency of this infection in most tropical countries.

Bacillary-dysentery carriers.—The "carrier question" in bacillary dysentery is hardly comparable with that in other infections, such as typhoid. Bacillary dysentery has a short incubation period and is essentially a localized disease. The bacilli remained confined to the intestines and to the mesenteric glands. Typhoid on the other hand is primarily a septicæmia with secondary localization in the intestines.

There are many circumstances which render the "carrier state" in bacillary dysentery difficult of detection. Dysentery bacilli, as a rule, are scarce and liable to escape detection in a fæcal stool. We are still without very accurate statistics upon the frequency of the carrier state, but it appears probable that carriers are responsible for the starting of an epidemic. The majority of recognized carriers in bacillary dysentery are "*convalescent carriers*," a term which implies that the victims have incompletely recovered from the disease and are still passing blood and mucus containing dysentery bacilli in the stools. The healthy carrier in bacillary dysentery is rare. There is no evidence that the gall-bladder acts as a reservoir of infection, as in typhoid; and in fact the "carrier state" does not persist for any great length of time. The organisms persist in retention cysts in the intestinal mucosa, in collections of pus from beneath the scars of ulcers and in collections beneath the edges of chronic ulcers. The carrier state usually lasts four to six months from the onset, and at the end of a year most have ceased to be infected. The maximum period the carrier state can last is three years. A carrier state supervenes in about 3 per cent. of recovered cases of bacillary dysentery.

Carriers of Flexner bacilli are much more frequent than those of the Shiga bacillus. Generally the average Flexner carrier is in good health, while the Shiga carrier is an invalid.

There is a condition in which bacillary inflammation or ulceration is localized in the lower portion of the rectum; patients often involuntarily pass viscid blood and mucus, though otherwise in good health, and the bacillus may be isolated, by means of swabs from the rectum, after a lapse of three years from the initial attack. Probably the *formes frustes*, or the slight and clinically almost unrecognizable forms, play an important rôle in its spread.

Simple microscopic examination of the fæces affords little assistance in these cases. The chances of isolating the specific bacillus are considerably increased by making cultures direct from the mucosa by rectal swabs, or from scrapings of ulcers obtained through the sigmoidoscope. An apparatus,

known as Ziemann's tube, is used for this purpose. It is a glass tube 28 cm. in length by 2 cm. in diameter, and situated 3 cm. above the lower end, which is closed as in a test tube, is a circular opening 1·5 cm. in diameter. When it is desired to obtain a sample of intestinal contents, the rounded end is introduced into the rectum and pushed gently upwards with a rotatory movement, with the result that some of the fæces pass into the lumen through the lateral aperture.

Dysentery bacteriophage.—D'Herelle originally made the observation that a filtrate of a convalescent dysentery stool developed the property of clearing a broth culture of Shiga's bacillus, but when a culture which had been dissolved in this manner was filtered, and a few drops were added to a fresh culture, the bacilli were again dissolved and that this process could be repeated indefinitely. Shiga's bacillus is the organism which was first recognized as susceptible to bacteriophagy. The bacteriophage itself consists of ultra-microscopic particles having dimensions of 20–30 $m\mu$ (millimicron). It is apparently true that there are many races of bacteriophage which are virulent for Shiga's bacillus, but the bacteriophage obtained from the Flexner bacilli is apparently virulent solely for members of that group. Bacteriophage has been isolated from the stools of patients convalescent from bacillary dysentery, and from the stools of mild cases. It appears probable that improvement in the clinical condition of the patient coincides with the increased virulence of the bacteriophage in the stools which then dominates the dysentery bacilli. On these data a dysentery bacteriophage has been prepared for therapeutic use.

Diagnosis.—Difficulty in the diagnosis of bacillary dysentery on clinical grounds is mainly confined to the milder forms. Whenever possible a laboratory diagnosis should be made.

The possibility of malaria occurring in the course of bacillary dysentery should always be borne in mind. Dysentery very often awakens a quiescent malaria fever, usually of the benign tertian form. The concurrence of a subtertian infection with bacillary dysentery is a particularly serious combination.

Generally, a tentative diagnosis may be made from a microscopic examination of the *cellular exudate* in the stools—that is, if the distinctive cellular picture is obtained—a method now known as cyto-diagnosis. For this purpose the specimen should be procured fresh, from the patient and as early as is possible in the disease. The characteristic feature of the bacillary stool, as seen under the microscope (Plate XIV), is the preponderance of swollen *polymorphonuclear leucocytes*, with distinctive ring-like nuclei ; they constitute over 90 per cent. of the total cell elements in the stool. The examination should be conducted with a $\frac{1}{6}$-in. lens and a low ocular ($\times$ 2).

Macrophage cells.—These cells, sometimes 20–30 μ in diameter are apparently derived from a proliferation of the endothelium of the capillary vessels of the gut. In shape they may be round, oval, or even bilobed. They are hyaline in appearance, and contain in their substance vacuoles and fatty granules, ingested red blood-corpuscles, or even occasionally leucocytes. They are non-motile, but, owing to

their phagocytic activities, are apt to be mistaken for *Entamœba histolytica*—an error often made by the inexperienced.

The differential-cell picture in dysenteric exudates is termed by Alexeieff a "pyogram." In amœbic dysentery the cellular elements are few and mononucleated; in bacillary dysentery, numerous and polymorphonuclear. The nuclei of the polymorphonuclears are *pseudopyknotic*.

It appears to be more important than ever that the significance of macrophage cells in bacillary dysentery stools should be emphasized. This tendency to diagnose amœbic dysentery upon a shred of evidence is very pronounced in almost every tropical country. It is most important that the pathologist should acquaint himself with the appearance of inflammatory cells which appear in the fæces, as well as with the different stages of the dysentery amœba, before an expert diagnosis can be given. The main features of the cyto-diagnosis of dysentery stools were pointed out by the Editor in 1912 and this method was practised by him during the Great War, during which time it received ample confirmation.

Findlay has obtained assistance in differential diagnosis by the iodine reaction of the polymorphonuclear leucocytes and the production of nuclear-pseudopodia. The occurrence of a well-marked iodine reaction with nuclear-pseudopodia suggests a bacillary infections: their absence amœbiasis.

Entamœba coli and the flagellate protozoa (*Chilomastix* and *Trichomonas*) may be present in considerable numbers in a bacillary-dysentery exudate, especially during the convalescent stages. Difficulty may be experienced in differentiating *E. coli* from *E. histolytica* in a bacillary-dysentery stool, and may lead to the suspicion that one is dealing with a double infection of two diseases.

Isolation of the dysentery bacillus.—With practice this becomes a comparatively simple matter. The stool should be collected in a bed-pan, *which should contain no disinfectant*, and the patient should be warned against passing urine at the same time; a portion of freshly-passed blood and mucus should be picked out of the mass by means of a platinum loop, and, if soiled with fæces or urine, should be shaken up in 5 c.c. of distilled water or normal saline solution. The earlier in the course of the illness, the easier it is to isolate the dysentery bacillus. It is, as a general rule, difficult to do so after the dysentery has lasted five days. In sending specimens for laboratory examination through the post, or by messenger over long distances, the fæces should be emulsified with a double volume of 30-per-cent. glycerin in 0·6-per-cent. saline solution (Teague and Clurman), or, better still, with an equal volume of $\frac{N}{33}$ NaOH solution which, by rendering the medium alkaline, conserves the vitality of the organisms for a longer period (Dudgeon). It must be remembered that the organism is very delicate, and never occurs in great profusion even in a freshly-passed stool. The mucus, or two loopfuls of the suspension, should be spread, in a spiral manner, somewhat thickly upon a MacConkey agar plate; some prefer Conradi-Drigalski, others plain litmus-lactose agar, for this purpose. A preliminary incubation of the specimen in broth is not to be recommended, as the dysentery bacillus is so easily overgrown by other organisms of the *Bacillus coli* group.

The plate, spread in this manner, should be incubated at 37° C. in an inverted position for eighteen hours, and the small blue transparent colonies then examined with a watchmaker's lens. As a general rule, Shiga colonies are more refractile and of a more regular outline than are those of the Flexner-Y group. In order to make their recognition still easier, it is a good plan to hold a finger or a piece of dark paper against the back of the plate.

Identification of the colonies may be carried out as follows: Four or more should be picked off with a platinum spud and transplanted on to agar slopes, and, after a suitable incubation period, these subcultures should be emulsified and tested in high dilutions against specific Shiga and anti-Flexner-Y serums in agglutination tubes. Should the method of macroscopic agglutination be utilized, these serums will be found very specific, so that either on a microscope slide or on the agglutinometer (p. 1036) agglutination rapidly occurs.

As a measure of practical importance, a method of preliminary agglutination may be employed. Ten or more suitable colonies are picked off the plate by a platinum spud or small loop, and emulsified in a very small quantity (0·25 c.c.) of normal saline; a rather thick opalescent emulsion results. By means of a capillary pipette, drops of this emulsion are placed together with an equal quantity of the specific serums diluted to 1 : 50. The resulting dilution of the serums will then be 1 : 100. The test may be performed either on a microscope slide or on the agglutinometer. After oscillation for three minutes, should the reaction be positive, snowflake agglutination occurs.

After these preliminary measures the diagnosis may be confirmed by inoculating subcultures of the organism into the sugars (Table, p. 499).

Isolation of the dysentery bacillus post mortem.—The bacillus can be isolated with ease from the acutely inflamed mucosa by washing the canal free from intestinal contents and scraping off the blood and mucus with a platinum loop. From the mucosa which has undergone coagulation necrosis this is by no means easy. In this case the surface must be first seared with a hot knife or glass and incised; the material for culture is then obtained with a platinum loop from the bottom of the incision.

The bacillus may occasionally be recovered from the inflamed mesenteric glands, but not usually from the bile, liver, spleen, or any solid organ.

Serological diagnosis.—This is of little value as an aid to diagnosis in the early stages of the disease, or in the very acute or rapidly fatal types in which it is so important to arrive at an accurate opinion. The serums of some patients, proved to be suffering from bacillary dysentery by isolation of the specific organisms from the stools, may give a negative agglutination reaction, and, further, certain normal serums have the power of agglutinating the bacilli in low dilutions.

For the diagnosis of Shiga infection, say in convalescent or chronic cases, an agglutination of over 1 : 25 should be obtained. In Flexner infection an agglutination of 1 : 100 is sufficient for a positive diagnosis. A. Davies found dysenteric agglutinins were present in dysenteric stools, even when absent from the serum of the patient, especially during the first week of the illness. The blood and mucus are shaken up with normal saline and filtered.

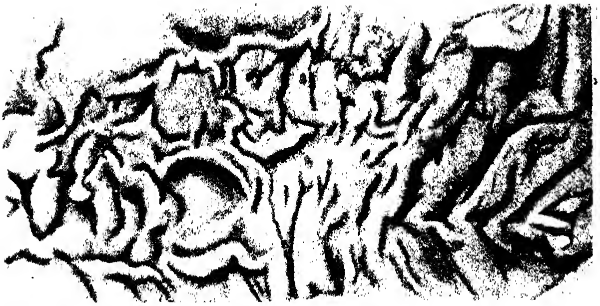
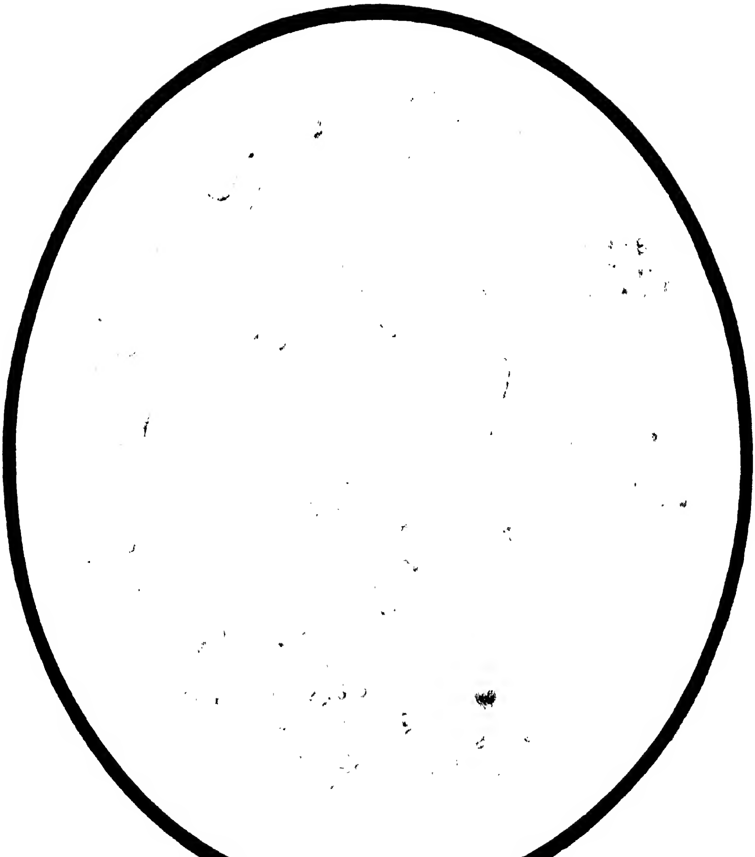


Fig. 1. AMŒBIC DYSENTERY. Typical patches of infiltration and ulceration of ascending colon, showing "Dyak-hair" sloughs. Fig. 2.—BACILLARY DYSENTERY (Sonne infection): Acute Sonne dysentery in a child, showing bright pink hyperæmia of muscular coat. Fig. 3. BACILLARY DYSENTERY (Shiga infection): Coagulation necrosis of lower portion of ileum, showing characteristic gree coloration of the destroyed mucous membrane.

INTESTINAL LESIONS IN AMŒBIC AND BACILLARY DYSENTERY (*Half nat. size*).

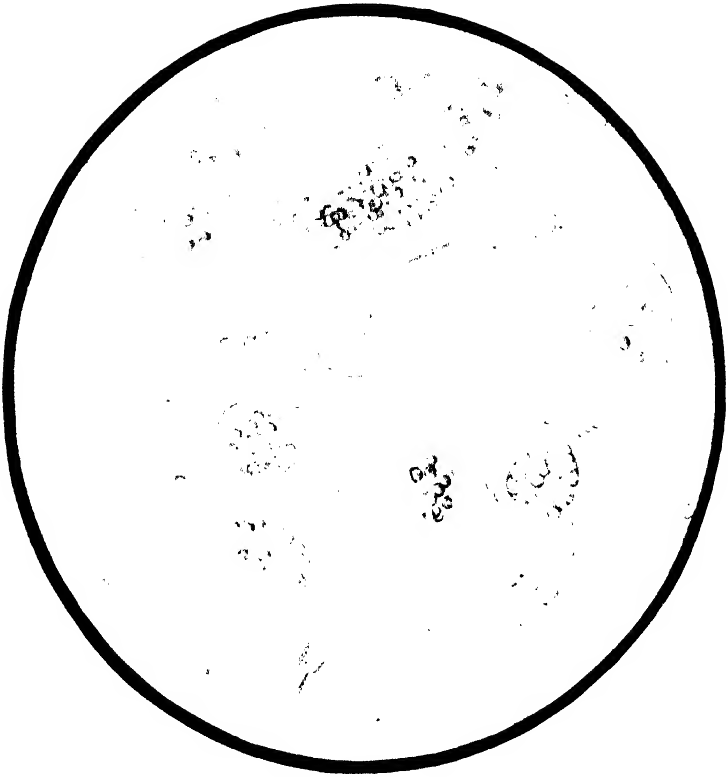
PLATE XII



MICROSCOPIC APPEARANCE OF CELLULAR EXUDATE IN ACUTE BACILLARY DYSENTERY (Shiga infection).

Fresh preparation. Shows macrophage cells with ingested red blood-corpuscles, intestinal epithelium and polymorphonuclear leucocytes.

PLATE XIV



MICROSCOPIC APPEARANCE OF EXUDATE IN AMŒBIC DYSENTERY.

Fresh preparation. Shows active Entamœba histolytica. Some with ingested red blood-corpuscles, acicular Charcot-Leyden crystals and disintegrated intestinal epithelium.

Plate XV

Fig. 1. Acute bacillary dysentery Shiga infection. Note œdema of mucosa and submucosal hæmorrhages.

Fig. 2. Chronic bacillary dysentery Flexner infection. Note granulations on mucous membrane.

Fig. 3. Acute amœbic dysentery. Note folding of lax mucous membrane, pin-point ulcers and surrounding submucous hæmorrhages.

Fig. 4. Chronic amœbic dysentery. Note diamond-shaped ulcers and submucous hæmorrhages.

SIGMOIDOSCOPIC APPEARANCES OF RECTUM IN BACILLARY AND AMŒBIC DYSENTERIES.

Serological diagnosis may be of considerable assistance in chronic bacillary dysentery where high-titre agglutinations are sometimes obtained, especially with pooled emulsions of the V, W, X, Y, and Z strains of Flexner's bacillus. The serological diagnosis of Sonne dysentery by means of the agglutination test is also somewhat unreliable. It appears to depend, to some extent, on the strain of the organism employed as antigen.

Sigmoidoscopic examination.—The sigmoidoscope is especially useful in chronic cases, and should be employed wherever practicable. For preparation of the patient, a cathartic of ½ oz. of castor oil is given; the following morning the bowel is cleared out by means of a warm-water enema. If the patient has acute diarrhœa, the omission of castor oil is advisable. In any case it should not be given later than 2 p.m. on the day preceding the examination. It is advisable to give 10–15 min. of tincture of opium half an hour before the examination, in order to render the rectum less sensitive. The mucous membrane of the rectum is seen to be replaced by granulation tissue with surrounding hyperæmia which has a characteristic appearance resembling the cortex of a granular kidney after the capsule has been stripped; at the same time infiltration and thickening of the bowel-wall can be made out (Plate XVI). Seldom are ulcerations seen in chronic cases. The passage of an instrument is attended by pain due to distension of the bowel wall, and this in itself is almost diagnostic, as amœbic ulceration of the bowel is almost entirely painless.

An intradermal test has been introduced by Brokman: 0·1 c.c. of Shiga-dysentery toxin in a dilution of 3 : 100. A very considerable reaction is produced at the end of twenty-four hours, when a diffuse red infiltration appears, afterwards turning blue; sometimes an ulcer forms. This reaction becomes negative after the injection of antidysenteric serum. A primarily negative reaction indicates the presence of sufficient antitoxin in the body to neutralize the dysenteric toxins.

Diagnosis between Bacillary and Amœbic Dysentery

BACILLARY DYSENTERIES	AMŒBIC DYSENTERY
Acute diseases with a tendency to epidemic spread. "Lying down dysentery."	A chronic endemic disease. "Walking dysentery."
Incubation period a short one, 7 days or less.	Incubation period a long one, at least 20–90 days; it may be more.
Onset acute.	Onset insidious.
Pyrexia common.	Pyrexia rare, unless complicated.
Course days or weeks.	Course usually prolonged for years.
Complications: Polyarthritis frequent; eye complications.	*Complications:* Hepatitis, abscess of liver, abscesses more rarely in other situations. Pericolic abscess.

DIAGNOSIS BETWEEN BACILLARY AND AMŒBIC DYSENTERY
(*Continued*)

BACILLARY DYSENTERY	AMŒBIC DYSENTERY
Death due to— (*a*) Exhaustion. (*b*) Toxæmia.	Death due to— (*a*) Exhaustion. (*b*) Perforation. (*c*) Hæmorrhage. (*d*) Liver abscess.
Signs : General tenderness over whole abdomen, more marked over sigmoid flexure.	*Signs :* Local tenderness and thickening, mostly over sigmoid flexure, transverse colon, and cæcum.
Tenesmus very severe.	Tenesmus not usually noted.
Pathology : Acute diffuse necrosis of mucous membrane of large intestine, due to toxins of the dysentery bacillus.	*Pathology :* Local lesions confined solely to the large intestine, due to the characteristic ulcers.
Ulcers : When present, on free edge of transverse folds of mucous membrane and distributed transversely to long axis of gut.	*Ulcers :* Commence as small abscesses of submucosa distributed in long axis of gut. " Flask-shaped ulcer," or *Bouton en chemise* (" sea anemone " ulcers).
Serpiginous in outline, with ragged undermined edges, often communicating with neighbouring ulcers ; bases consist of granulation tissue.	Oval in shape, regular in outline ; flask-shape in section, involving all coats ; bases consist of necrotic black tenacious sloughs (" Dyak-hair " sloughs).
Intervening mucous membrane hyperæmic. Ulcers rarely perforate. No compensatory thickening of bowel-wall.	Not uncommonly perforate ; compensatory thickening of bowel-wall. Intervening mucous membrane not affected.
Stools : Scanty ; many in number. Bright blood-red, gelatinous, viscid mucus, odourless, resembling red-currant jelly.	*Stools :* Fæces intermingled with blood and mucus, resembling anchovy sauce (sago-grain stool). Very offensive, smelling of decomposing blood ; generally copious.
Reaction : Alkaline.	*Reaction :* Acid.
Microscopic picture : Numerous red cells ; polymorphs numerous, with clear-cut ring nuclei. Macrophage cells may be numerous. Few visible micro-organisms (Plate XIV).	*Microscopic picture :* Red cells numerous and in clumps, polymorphs much damaged, often extruded nuclei. Macrophage cells scarce. Large numbers of motile bacilli, *Entamœba histolytica,* generally with ingested red cells. Charcot-Leyden crystals common (Plate XV).
Blood examination : No leucocytosis in the early stages.	*Blood examination :* Usually a moderate leucocytosis.

The wider subject of differential diagnosis of the various dysenteries will be dealt with on p. 566.

Prognosis depends very much upon the susceptibility and physical condition of the person attacked. In the jails of India, in fact throughout that country, though bacillary dysentery is widespread, the case-mortality is very small indeed. Of the many thousands of cases among British troops in the Great War, it is doubtful whether it at any period rose above 5 per cent. Epidemics in native races have been recorded where the mortality was over 28 per cent., and others among debilitated natives, as, for instance, Solomon Islanders, in which it was 47 per cent. Prognosis is bad in chronic cases, especially is this the case in poverty-stricken, malaria-infected, half-starved natives.

Treatment.—The patient should be placed in bed on the appearance of the first signs, and should on no account be permitted to get up in order to pass his motions. A bed-pan should therefore be employed wherever nursing facilities are available. In the choleraic or fulminating cases in which the passage of stools is incessant, and the physical exhaustion consequently very great, it may be advisable to dispense with a bed-pan altogether. The patient should then be placed upon a waterproof sheet and the buttocks well padded with tow, which, when soiled, can be collected and burned. For this purpose the attendant, for self-protection, should wear rubber gloves, as the discharges are highly infectious.

Arrangements should be made for the periodic inspection of the stools, for by these, supplemented by the appearance of the tongue and the general condition of the patient, the progress of the case can best be ascertained.

Considerable attention should be paid to the diet, which should be nutritious and easily assimilable, leaving as little residue as possible. Modern medical opinion is strongly opposed to milk in the routine treatment of bacillary dysentery. Whether plain, boiled, or peptonized, it is apt to curdle in the intestinal canal, and the casein clots thus formed have to be passed in the stools. The best diet is one consisting of jellies, albumin water, rice water, chicken conjé, beef tea, Brand's essence, Eatan (a pre-digested meat-juice), arrowroot, sago puddings, any of which may be given at two-hourly intervals in small quantities (6–10 oz.), slightly warmed, at each feed. Physical exhaustion necessitates a nutritious diet ; it is therefore inadvisable to attempt to feed dysenterics over a long period on albumin water.

In every case, even in the most severe, treatment should be preceded by a mild purge ; the most suitable for the purpose being castor oil, to which tincture of opium (15 min.) may be added. The routine treatment with saline aperients has received general commendation. The best salt for the purpose is sodium sulphate in drachm-doses exhibited two-hourly for the first two days, afterwards every four hours until the stools become fæculent. Some clinicians prefer routine treatment

with castor oil or rhubarb, which is given in drachm-doses hourly for eight doses till the third or fourth day of the illness; subsequently saline purges are given. It is thought that the castor oil provokes peristaltic action. In the case of small children liquid petroleum (nujol) in small doses should be given every two hours while the patients are awake. Hydrolax is recommended as a suitable preparation.

Opium.—It is permissible to exhibit opium, either by the injection of morphia or in solution, as a means of promoting sleep and relieving pain, if very severe.

Bolus alba (kaolin).—As a means of checking the diarrhœa and of eliminating the dysentery toxins in the intestinal canal, a mixture of animal charcoal and kaolin has been utilized in Germany and in Austria; the powder should be given suspended in water in doses of three teaspoonfuls every few hours. Crookes's collosol kaolin has much the same effect.

Targesin, a complex colloidal combination of albumin with diacetyl-tannic acid silver salt, is said by Lippelt to give favourable results. The dose is two tablets by the mouth three times daily. It is said to abolish the bacilli in carriers of bacillary dysentery.

Rivanol, an intestinal disinfectant (see p. 543), *has been used in* epidemics as a mass treatment of bacillary dysentery. Adults should receive 0·1 grm. in tablet form (rivanolettes) three times daily, and children correspondingly smaller doses. Rivanol has the advantage of being cheap and does not produce any untoward effects. It is said that serious epidemics of bacillary dysentery may be cut short by this treatment.

Other drugs.—The administration of massive doses of bismuth has many advocates. It is given in drachm doses every three hours during the acute stage. The carbonate or salicylate, not the subnitrate, should be used.

Anti-dysenteric serum.—The best-known serums are those prepared by the Lister Institute; similar ones are made by Burroughs Wellcome, Mulford, the Rockefeller Institute, the Berne Institute, by Shiga in Japan, and Dopter in France. The action of the serum is to be regarded as purely antitoxic rather than antimicrobic. The idea underlying its administration is that of neutralizing the toxæmia and of preventing, if possible, necrosis of the mucosa. It is much easier to produce a potent and effective anti-Flexner serum than an anti-Shiga one. When necrosis has occurred, it is doubtful whether the serum has any effect whatever. Not every case of bacillary dysentery necessitates antiserum treatment. The indications for the injection should be based upon consideration of the patient's condition, the number of stools, the pulse, the abdominal pain and the passage of more than twelve to eighteen stools in the twenty-four hours. An efficient anti-Shiga serum has now been prepared and can be obtained in concentrated form.

There are various routes by which the serum may be administered.

In very severe or fulminating cases it is best given *intravenously* by the open method, in doses of 50–60 c.c. diluted with a pint of saline. The fluid should be injected slowly, at least ten minutes being spent in the process. It is advisable to warm the diluted serum to 99 – 100° F. before injection, and, if a deposit is present, to strain it through a piece of sterile linen or sterilized filter-paper.

Owing to the possibility of hypersensibility (anaphylaxis)—which, though occurring rarely, may be attended by fatal results, especially after intravenous injection—it is advisable to inquire whether horse-serum has been administered to the patient at some previous period.

Either the median cephalic or the median basilic vein should be chosen. The veins can be made prominent by means of a rubber tourniquet, or even by digital pressure. It is usually unnecessary to incise the skin.

The serum is absorbed much more quickly by the *intramuscular route* than when given subcutaneously. A convenient site is the adductor muscles of the thigh; the needle should be inserted at a point well internal to the femoral artery. A large-bore needle should be used.

The sites generally chosen for *subcutaneous injection* are the flanks, between the crest of the ilium and the costal margin, or the lax tissues over the lower part of the abdomen. The pain, which results from the distension of the tissues when 100 c.c. or more are given, constitutes a disadvantage of this method. If the toxic symptoms do not abate, a second injection may be given forty-eight hours after the first.

In children, who become rapidly poisoned with dysenteric toxins, the *intraperitoneal route* is recommended. The serum, 10–30 c.c., should be diluted with 150 c.c. of 5-per-cent. glucose in normal saline solution.

Care must be taken that the serum does not deteriorate after long storage. In the tropics especially, all curative serums should be stored in the ice-chest.

A week or more after the injection, *serum sickness* is apt to supervene. An urticarial rash is accompanied by pyrexia, malaise, and stiffness of the joints. To anticipate and prevent the advent of these symptoms, it is recommended that calcium lactate (20 gr.) should be given by mouth on the day of the injection and on two or three subsequent days.

Serum treatment is of little avail in the chronic form of the disease.

Bacteriophage treatment.—It is probable that natural recovery from an acute attack of bacillary dysentery is connected with production of a corresponding amount of bacteriophage in the intestinal canal to combat the infection. A potent anti-Shigaphage has been prepared by d'Herelle, Morison, and others, and it is particularly difficult to obtain accurate statistics as to the efficacy, or otherwise, of this substance. This phage is distributed in ampoules in quantities of 2 c.c. The patient takes three ampoules by the mouth daily. It may also be injected per rectum. Whenever this method has been subjected to

critical analysis, as in the work of Taylor, Greval, and Thant (1930), the results are inconclusive.

Relief of pain.—During the early stages of an attack the patient may suffer much from griping and tenesmus. These are generally relieved by a hot bath, or by hot fomentations, or turpentine stupes, three or four of which may be roughly sewn into a piece of flannel and laid on the abdomen. This application has the advantage of being very light, of not wetting the clothes, and of keeping warm for many hours. Tenesmus and dysuria are best relieved by morphia hypodermically ; or by an enema of a wineglassful of thin starch containing 40 or 50 drops of laudanum ; or by suppositories of morphia and cocaine. Washing out the rectum with a pint of very hot water, with or without boric acid, is sometimes effectual in removing for a time, or, at all events, of mitigating, the incessant desire to go to stool and to strain. Bismuth carbonate 2 dr., with tincture of opium 30 min. and thin starch 2 oz., is also a good sedative enema. Painful colic or peristaltic action may be counteracted by the following mixture :

℞ Tinct. belladonnæ	♏vii (0·414 c.c.)
Pot. brom.	gr.x (0·648 grm.)
Tinct. chlor. et morph. co. . . .	♏x (0·592 c.c.)
Syrup. aurant.	ʒi (3·55 c.c.)
Aq. menth. pip. ad	℥ss (14·2 c.c.)

Ft. mist. ℥ss t.d.s., p.c., vel p.r.n.

Collapse may occur at almost any stage, and may be due to physical exhaustion caused by excessive straining and loss of fluid. Every endeavour should be made to restore the balance by the intravenous injection of large quantities of saline and glucose.

Vomiting and hiccough in these severe cases should both be regarded as of serious portent.

Appendicostomy as a method of treatment.—This particularly heroic measure has been carried out under local anæsthesia in desperate cases of the choleraic type, with success, in a few cases. The large intestine is thereafter washed out through the appendicostomy opening with boracic-acid solution.

Treatment of complications.—*Arthritis* is best treated by application of Scott's dressing, by radiant heat, or by sand-baths at 45°–60° C.

When the joint is greatly distended the excessive fluid may be aspirated. *Iritis* is treated by atropine, the use of an eye-shade, etc.

Treatment of chronic bacillary dysentery cannot be considered very satisfactory, for the healing of a chronically scarred bowel is effected slowly and with difficulty, and, as in ulcerative colitis, pseudopolyposis may occur. The diet should be carefully regulated, and small doses of aperient salines given at regular intervals. Gentle abdominal massage over the course of the large intestine, in order to

promote normal peristalsis, may assist in relieving pain and in promoting nutrition.

Moro's apple dietary has been used extensively in Germany, both for adults and children, in chronic dysentery; twenty or more apples made into a purée are eaten daily. A preserved apple powder, *Aplona*[1], is made in Switzerland. In grave cases nothing besides Aplona is given for three days. The dose for adults is 1–1½ oz. (3½ oz. of Aplona = 360 calories), and the amount required for a day is divided into portions, each of which must be freshly prepared with boiled water at drinking temperature, or with weak tea, 60–120 gr. to ¼ pint of liquid. It must not be brought to boiling point and no sugar should be added, but saccharine may be used instead. After the third day Aplona may be added to gruel or milk, being first mixed to a smooth paste with water.

Rectal irrigation.—Apart from operative measures, described below, the most hopeful method of treating the chronic form of the disease is to irrigate the affected surface of the large bowel with various antiseptics, with the object of cleaning the gut and stimulating the processes of repair. The following apparatus is required:

(1) A glass funnel, which should be cylindrical in shape, 1½ in. in diameter, and so graduated as to hold 10 oz. of fluid. The lower part should be provided with a constriction so as to accommodate the rubber tubing and to afford a firm grip. The tubing itself should be bound round with a tape ligature.

(2) Rubber tubing ½ in. in diameter; a length of 3 ft. is required.

(3) Rectal tube. This should be a stout catheter at least ⅜ in. in diameter, with a big round terminal opening.

(4) A bulbous glass tube for joining the tubing to the rectal tube.

(5) Narrow tape, necessary for tying securely all the junctions.

(6) Rubber gloves for the operator's hands, and a supply of vaseline.

Methods of administering the lavage.—The patient should be given ½ oz. of castor oil subsequently to his ordinary meal the previous evening, but on the morning of the irrigation only a light breakfast should be permitted. A large enema of sodium bicarbonate solution (1 dr. to the pint) should be given to clear out the bowel about half an hour before the irrigation is due. The apparatus should then be fitted together, securely tied, and sterilized. The temperature of the fluids used for irrigation should be 100–110° F.

When the patient is reasonably robust, the irrigation can best be administered in the genupectoral rather than in the left lateral position; this point, however, is of little real importance, and should never be allowed to outweigh the distress caused by the former position to a weak and toxic patient. In severe cases the preparation of the bowel, which is at the best an exhausting process, should be abandoned altogether, for in such cases the sphincteric action may be so weak that the irrigation has to be performed while the patient is suitably padded or is placed on a bed-pan. It is best to elevate the foot of the bed slightly. The rectal tube is well greased with vaseline, the apparatus filled with fluid, and the tubing constricted while the tube is gently inserted for a distance of about 3 in.; further introduction of the tube only results in excoriation of the inflamed mucosa, kinking of the

[1] Sold by Coates and Cooper, 94 Clerkenwell Road, London, E.C.1.

tube, stimulation of peristalsis, or, possibly, perforation ; the so-called " high " rectal tube is worse than useless. The funnel is held so that the fluid level is about 1 ft. above the anus, the tubing is then released and the rate of flow carefully regulated ; the correct rate is 1 in. of fluid per minute, and this can easily be adjusted by raising or lowering the funnel for a distance of about 2 ft. The tube itself should be held in the rectum throughout the operation, for if this is not done it may be extruded. Lateral pressure on the buttocks aids the retention of the injection, especially when the patient himself feels that he has taken all he can manage. The patient should be encouraged to put up with the discomfort and retain the injection as long as he possibly can. Where appendicostomy has been performed, the irrigation may be carried out through a catheter, size No. 10, introduced *via* the appendix. The patient should be placed upon a bed-pan and cautioned to contract the anal sphincter as little as possible, so as to permit the injection to flow through the large intestine as freely as is possible. It is best given on alternate days.

The best method of internal medication in chronic bacillary dysentery consists of using eusol as a *retention* enema by injecting 10 ounces, consisting of equal parts of eusol and water. Whenever it causes pain the eusol should be further diluted. Kamillosan (chamomile, *Matricaria chamomilla*), a preparation obtainable from Homburg, has a soothing effect on the bowels. One teaspoonful to eight ounces of warm water should be injected as a retention enema.

Willmore has advocated an " etherol retention enema " consisting of olive oil 12 ounces with 6 drachms of ether, to be injected in the evening with the foot of the bed elevated, and to be retained all night.

Washing out with hypertonic saline solution and adding one drachm of eusol to the pint is found excellent treatment. The addition of a small quantity of ox-bile to normal saline solution causes a contraction of the bowel-wall. Other methods consist of the addition of equal parts of salicylate of soda, biborate of soda and common salt (1 drachm) to the pint of water. Another effective means of irrigation is by means of linseed 6 ounces to 8 pints of water boiled for two hours, strained, and injected slowly in quantities of 6–8 ounces. Bismuth subgallate, 5 per cent. in olive oil at body temperature in retention enemata of 8–10 ounces each and administered for 10 consecutive treatments, is also useful.

The following substances are used for irrigating the bowel :

Substance		*Approximate strength*
Sodium chloride .		dr. 4 to pt. 1 (1 : 40)
Sea-water . .		— pt. 1
Sodium bicarbonate	Normal saline	dr. 4 ,, pt. 1 (1 : 40)
Eusol . .	Water	oz. 5 ,, pt. 1 (1 : 4)
[1] Protargol or albargin (argentum proteinate, B.P.)		gr. 100 ,, pt. 1 (1 : 100)
Tannic acid .		gr. 100 ,, pt. 1 (1 : 100)
Copper sulphate .		gr. 100 ,, pt. 1 (1 : 100)
Silver nitrate .		gr. 75 ,, pt. 1 (1 : 150)
Yatren (Quinoxyl)		grm. 5 ,, oz. 8 (1 : 40)

Surgical treatment of chronic bacillary dysentery.—When less heroic methods fail, and the patient's condition is slowly but progressively

[1] Not recommended. Silver protein salts are very expensive and are only soluble in cold water.

deteriorating, right inguinal colostomy offers a reasonable chance of success. If so serious an operation is declined, *appendicostomy* may be urged. The cæcum and colon may now be washed out with normal saline, or with an astringent solution, such as tannic acid, through the appendix, as frequently as desired. For this purpose a No. 8 rubber catheter with a copper stylet is employed, and rectal tube with an outflow tube. The patient should lie on his back; but should the cæcum get distended and the fluid fail to pass freely, turning to the left will restore the flow.

Cæcostomy and ileostomy.—In cases with pseudopolyposis of the mucous membrane and incessant distressing blood-stained diarrhœa, the operation of valvular cæcostomy should certainly be given a trial. The results have been eminently successful in some cases which were incurable by medicinal means (A. L. Gregg). A Paul's tube is at first inserted into the cæcum and the fæces are allowed to escape through it, thereby placing the whole of the large intestine at rest. Then an efficient opening is made. The lower bowel may be washed out daily with boric-acid solution, and the opening may be closed at some subsequent period, after the large bowel has been permitted to rest for three months or more, and complete recovery of the mucous membrane has been observed to take place by sigmoidoscopic examination. A colostomy bag is fitted. The patient may be sent to convalesce and encouraged to consume plenty of fresh eggs, milk, fruit, etc. One-barrelled ileostomy is sometimes preferable and is recommended by some surgeons. The indications here are the same as in ulcerative colitis, but it condemns the patient to a permanent colostomy belt and other disagreeable sequelæ.

Ispaghula.—The boat-shaped seeds of *Plantago ovata* have acquired a popular reputation in the treatment of chronic dysentery in India. The seeds are either chewed, when a gelatinous substance exudes which acts as a demulcent, or the pericarp is made into a paste, which is sold as "chilka" in the bazaars of Bombay. If taken in 1-dr. doses three times daily, it has a soothing effect. Chopra has shown that these seeds contain a glucoside *aucubin*. The mucilage which exudes from the seeds is acted upon by the digestive enzymes and coats the inflamed mucosa. Iso-gel (Allen & Hanbury) has much the same effect.

Prophylaxis.—The prophylaxis of bacillary dysentery consists principally in securing a pure water supply and in avoiding unwholesome and contaminated food. In barracks, camps, lunatic asylums, and other public institutions, bacillary dysentery should be regarded as an infectious and readily communicable disease, and therefore patients suffering from mild symptoms, or even looseness of the bowels, should be isolated.

In order to prevent the spread of bacillary dysentery in closely crowded communities, it is important to recognize, as early as is possible, all carriers of the infection and mild cases of the disease, which might otherwise escape recognition. Cunningham and others have pointed out that in the prevention of the spread of bacillary

dysentery in jails, it is most essential that the stools of the inmates should be inspected macroscopically daily. Any inmate found passing blood and mucus, even in small quantities, should be regarded as potentially infectious and as possibly constituting a carrier of the disease.

The chronic dysentery carrier is the most difficult to deal with. These cases should be isolated and treated with vaccines. Kolmer treats such cases by vaccines given at first subcutaneously and subsequently intravenously. The initial dose is one million bacilli, and this is subsequently increased to five and ten million organisms. Treatment by sulphanilamides may possibly prove to be more effective.

Prophylactic inoculations.—The Japanese, and later Gibson, introduced an inoculation by which the toxic effects of the bacillus are neutralized by the addition of a potent anti-Shiga serum, resulting in an almost complete absence of reaction. The vaccine and serum (sero-vaccine) are put up in twin phials, the bacillary emulsion being contained in one arm, the serum in the other. The first dose is 0·25 c.c., containing 500 million Shiga organisms mixed with 0·1 c.c. of serum; the second dose, given 10 days later, contains 1,000 million organisms with 0·2 c.c. of serum.

The limited number of statistics available are distinctly in favour of this method of protection. A somewhat similar method has been applied in Germany and in Austria under the name of "*Boehncke's Dysbakta.*" Besredka produced an antidysenteric bili-vaccine consisting of dead dysentery bacilli with the addition of bile. The technique is to give on three successive days before breakfast a dose of bile, followed by a pill containing the desiccated vaccine. Two hours before the first meal of the day, a tablet containing 20 c.gm. of desiccated bile is administered orally and this is followed by a dose of 100 milliards of dysentery bacilli killed by heat. No food is allowed for two hours after the dose and the same treatment is given on two further consecutive days.

Blanc and Caminopetros employed intramuscular injections of *living vaccines* consisting of 4–6 thousand million dysentery bacilli, and found that they caused a slight infiltration to appear which resolved again in three or four days. They concluded that no danger existed in using a living vaccine.

II. AMŒBIC DYSENTERY AND AMŒBIASIS

Definition.—Amœbiasis is a term employed to indicate an infection with a protozoan—*Entamœba histolytica.* When the activities of the parasite are confined solely to the intestinal canal it produces *amœbic dysentery,* or primary intestinal amœbiasis, a disease insidious in its onset, chronic in its course, and with a marked tendency to relapse. When metastatic lesions develop in the liver it is known as secondary amœbiasis, or *hepatic amœbiasis.*

Geographical distribution.—Amœbiasis occurs to a greater or lesser degree throughout the tropics and subtropics. During recent years sporadic indigenous cases have been reported from Northern Europe and even, very rarely, in Great Britain. Specially prevalent in India, Indo-China, China, and the Philippines, it is common throughout North and Central Africa, and widespread in the Southern United States, South America, and the West Indies.

Epidemiology and endemiology.—Amœbiasis arises sporadically without any particular seasonal prevalence, and does not usually occur in epidemic form in the same manner as in bacillary dysentery. As in the case of bacillary dysentery, house-flies may play a considerable part in dissemination. The work of Wenyon and O'Connor has shown that, not only can the cysts of *E. histolytica* be demonstrated in the fæces of wild flies, but that they continue to be passed by experimentally-infected insects for sixteen hours or longer. There is also evidence to show that *contaminated water* and fresh vegetables, such as lettuce, may constitute suitable vehicles of infection. The latest reports of the outbreak in Chicago in the summer and autumn of 1933 give the total number of cases as 1,409 occurring in that city or traced to other cities in the United States, with over 40 deaths. The source of the infection was traced to two hotels, where the majority of those infected were employed in the capacity of servants or were guests. All the carriers of *E. histolytica* were removed from their employment, but in spite of these measures, cases continued to develop amongst employees of one hotel, and the "carrier"-rate among them was found to be as high as 47·4 per cent. Further investigations revealed serious contamination of the water supply from drainage. The incubation period of the disease in this instance was shown to be from 7–15 days, even up to 77 days.

Considering the susceptibility of the cysts to desiccation, it is probable that dust and sand play no part in the dissemination of this disease.

Intestinal amœbiasis is a disease of adult life as a rule. It is rare to find it in European children under five years of age. The youngest patient the Editor himself has seen was seven years old. Among Egyptian children of the poorer class in Cairo, Perry and Bensted found that 13 per cent. of clinical dysentery was due to *E. histolytica*, and Biggam has seen acute amœbic dysentery with liver abscess in an infant three months old; C. Williams has found it in a negro infant of fifteen months on the Gold Coast. As the disease has a long incubation period and is acquired from contaminated water and vegetables, it is unlikely to occur among carefully nurtured children in whom the bacillary form is much more common. This fact should be borne in mind by tropical practitioners.

Intestinal amœbiasis in man, producing active symptoms, may be in evidence for many years. The Editor has seen cases which have lasted from thirty to forty years without seriously undermining the patient's health, so

tolerant are the tissues to this parasite. There appears to be also a difference in the incidence of intestinal amœbiasis in the sexes. Males, European and otherwise, are perhaps more prone to contract the infection. Gharpure and Saldanha (1930) have shown that in a series of over 400 post-mortem examinations the number of male cases is quite disproportional to the total number. Of amœbic dysentery and liver abscess, 90·6 and 93·8 per cent. respectively occurred in males; 9·4 and 6·2 per cent. in females. Below ten years of age the incidence of amœbic lesions was 0·9 per cent. and of liver abscess nil. The highest peak is reached in the decennial periods 20–40, with a proportion of about 30 per cent. of amœbic dysentery and 38 per cent. of liver abscess to the total number of post-mortems.

In Armenia, Zaturjan has shown that amœbiasis in children usually runs a much more benign course than in adults and rarely shows any serious complications. The cyst-carrier rate among them there is 6·7 per cent.

Ætiology.—The discovery of amœbæ in dysentery stools was made by Lösch in 1875, and since then the intestinal amœbæ have been the object of much study. They were originally regarded as a single organism,—*Amœba coli*—but it is now recognized, mainly as a result of the work of Schaudinn, Hartmann, Wenyon, and Dobell, that several distinct amœbæ occur in the intestinal canal of man, one of which, *Entamœba histolytica*, is pathogenic for man, while the others—*Entamœba coli*, *Endolimax nana*, *Iodamœba bütschlii*, and *Dientamœba fragilis*—are harmless saprophytic species. *E. histolytica* was originally cultured on egg-medium by Boeck and Drbohlav in 1925 (p. 1040), but during the last few years it has been grown on a variety of serum-media. This term Entamœba is used by most English authorities, though American writers claim that *Endamœba* is more correct.

Detection of entamœbæ in stools.—When present in stools, the entamœbæ are generally easy to find. All the preparation necessary is to pick out a small fragment of stool shortly after being passed, and then to lay this on the slide and compress it sufficiently under the cover-glass to form a fairly transparent film. It must be remembered that active entamœbæ tend to occur in clumps or masses and are not evenly distributed throughout the stool; they may be present in one motion and not in the next that is passed. Care should be taken that the receptacle in which the stool is collected for examination is free from all traces of antiseptics. The amœbæ live only for a few hours after being passed, and are readily distorted in the presence of urine. The dysentery amœba is a clear, faintly greenish-tinted, transparent body, as a general rule, some three to five times the diameter of a red blood-corpuscle. In its vegetative phase it is recognizable by its active movements, as well as by the presence in its interior of extraneous bodies, such as red blood-corpuscles, which it ingests. The nucleus may sometimes be detected in an eccentric position. The habit of ingesting red blood-corpuscles and body-tissue cells is one of the points of distinction between this amœba and the non-pathogenic *E. coli*.

In stained preparations[1] the body of the amœba is seen to be made up

[1] For the staining of amœbæ in liquid preparations *see* Schaudinn's method (Appendix, p. 1035). The details of amœbæ are distorted if attempts are made to dry the specimen as one would a blood-film.

of two zones—a granular endoplasm surrounded by a clear protoplasmic zone or ectoplasm. The nucleus shows a characteristic uniform structure if the specimen is fresh and fixed while alive ; aberrant forms with fragmented karyosomes, etc., are due to degenerative changes (*see* p. 857).

These amœbæ flow, rather than move, across the slide, and in the living state exhibit sometimes no very conspicuous differentiation between ectoplasm and endoplasm. They quickly die and degenerate when outside the body. Kept at a lower temperature for some time, they remain stationary ; when the slide is warmed, they eject from time to time hyaline " blade-like " pseudopodia. Degenerative entamœbæ often contain vacuoles, but such are not present in healthy specimens. When conditions are adverse, they encyst, but before doing so undergo a reduction in size with formation of precystic individuals.

Cysts.—Cysts vary much in size, and, according to Dobell and Jepps, *E. histolytica* is a species which is divisible, from the size of the cysts, into five distinct races. The smallest race produce cysts 7–9 μ in diameter ; the largest, 15 μ. At present there is no adequate evidence to show that these different races differ in pathogenicity. In their substance they contain highly refractile masses composed of chromatin, generally known as chromatoid bodies, which may assume the form of blocks with rounded ends, and also a glycogen-containing vacuole. When first formed, the cyst contains but one nucleus, which measures about one-third of its diameter ; this multiplies by binary fission, so that finally, in the more mature individuals, four small nuclei, each measuring one-sixth of the diameter of the cyst, are produced. In its general characters the cyst nucleus resembles that of the vegetative stage.

The cysts of *E. histolytica* can survive outside the body of man for about ten days if kept moist and cool. Desiccation kills them immediately, and they survive at a low much longer than at a higher temperature. The cysts will develop and exist under suitable conditions *in vitro* in Drbohlav's medium (*see* p. 1040). Thus the addition of a small amount of starch accelerates the process of encystation, while Dobell has found that the presence of certain bacteria favour the growth and multiplication of this protozoan, while some other species are harmful. A definite symbiosis appears to exist, and Dobell has found that cysts can neither develop nor hatch out in a sterile medium.

Westphal has recorded a significant experiment when an individual acquired a harmless *E. histolytica* infection by the ingestion of cysts. Some months later cultures of bacteria isolated from the fæces of acute amœbic dysentery were ingested and a similar dose was given to a control. Both the " carrier " and the control suffered from diarrhœa, but on the twenty-third day, the former developed clinical amœbic dysentery. It was afterwards possible to determine that the actual attack of amœbic dysentery was initiated by a Flexner infection.

Summary of life-history of Entamœba histolytica.—The active vegetative entamœbæ live on the tissues of the gut-wall, where they ingest blood-corpuscles and multiply by division. In the primary amœbic lesions the amœbæ make their way into the follicles of the large intestine where they multiply, and partly by pressure, partly by the secretion of a cytolysin, make their way into the interglandular tissue and produce a small amœbic abscess of the submucosa. In time

this abscess bursts and becomes an ulcer. A certain proportion of amœbæ leave the ulcers they produce, enter the lumen of the bowel, encyst, and pass out with the fæces. The precystic individuals, free from protoplasmic inclusions, are smaller than the ordinary forms which continue to multiply in the tissues. The typical cysts, smaller than the precystic forms, are quadrinucleate when mature. When swallowed by another human host they pass into the small intestine, where they hatch into amœbulæ which, in turn, attack and invade the tissues and recommence the cycle.

The above summary epitomizes the generally accepted account of the life-history of *E. histolytica*, but there are some observers, notably Reichenow, who consider that the entamœba is normally an inhabitant of the lumen of the intestinal tract and not a tissue-invader, but that, under certain conditions in the tropics, these amœbæ invade the intestinal wall and thereby give rise to amœbic dysentery. He thinks that the normal form is the *minuta* stage, which lives in the intestinal lumen, where it reproduces by binary fission and produces characteristic four-nucleated cysts. Westphal, on the other hand, regards *E. histolytica* as capable of both intra- and extra-cellular digestion. Proteolytic ferments, but no toxins, are produced.

A characteristic feature of amœbic infection of the intestine is the periodic variation in intensity, which may either be connected with resistance on the part of the tissues of the host, or possibly may be a feature in the development of the parasite.

Occasionally, however, the vegetative amœbæ may migrate from their site of election in the bowel-wall and, as tissue-invading forms, enter the venous system and be transported to the liver, exceptionally the spleen, brain, or lung; but by so doing they become unable to complete the cycle of development as observed outside the body, for pre-cystic individuals and cysts never develop in these situations. Amœbic infection of the skin around the sinus of a discharging liver abscess has been reported (*see* p. 563).

E. histolytica passers.[1]—The healthy passer (or excretor) of *E. histolytica* is an individual who has not suffered and is not suffering from dysenteric symptoms, but passes *histolytica* cysts, though otherwise in perfect health. Such cyst-passers may have active entamœbæ living in the tissues of the bowel.

The cyst-passers may now be divided into two classes—(1) the *contact* who has never suffered from amœbic dysentery, and (2) the *convalescent* who has recovered from such an attack. It is now known that, for every abnormal person who is suffering from amœbic dysentery with the passage of vegetative forms which are non-infective to others, there are large numbers of healthy persons who continue to pass *E. histolytica* cysts, and thus constitute a perennial source of infection. The vegetative entamœba must, in either case, live at the expense of the tissues of the host. We know from the post-mortem findings

[1] "Cyst-passer" is here used in the place of "carrier," a term which is not applicable to the life-history of *E. histolytica*.

in the Philippines and elsewhere that extensive bowel ulceration can occur without visible symptoms of dysentery having been present during life, and it is a matter of common experience that liver abscess may occur under these circumstances. The lesions of the mucosa may be of microscopic proportions. Cytolysis and necrosis of the superficial epithelium takes place and is followed in the majority of instances by rapid regeneration of the epithelium, so that the probability is that only a small percentage of those infected actually show clinical evidences of amœbic dysentery. The experiments of Walker and Sellards upon man showed that out of 20 men fed with *E. histolytica* 18 became parasitized, but only 4 developed dysenteric symptoms though the remainder continued to pass typical cysts in their stools.

By intrarectal and intracæcal injection of fæces containing cysts into cats and puppies, ulceration of the bowel-wall and even hepatic abscesses have been produced; but, although the fæces may be swarming with active vegetative forms, no cyst-formation has ever been observed in these experimental animals. Similar lesions can be produced in kittens by intrarectal injection of cultures of *E. histolytica.*

The infection in passers of *E. histolytica* is remarkably persistent, and in all probability, unless anti-amœbic treatment is instituted, these persons continue to pass cysts for the remainder of their lives.

Craig and other American authorities believe that everyone who harbours the cysts of *E. histolytica* is a candidate for some more serious complication due to this parasite, and that therefore every "carrier" should at once receive adequate treatment.

Incidence of cyst-passers.—Among British soldiers after a year's service in Egypt, Wenyon and O'Connor found that there was no marked difference between carriers who had previously suffered from dysentery and those who had not (the percentages being 6·5 as against 4·5 per cent.). The carrier rate among native Egyptians, as might be surmised, was found to be considerably higher, that is, 13·5 per cent. Perhaps the most surprising outcome of the systematic examination of fæces by protozoologists during the War is the almost universal existence of the histolytica carrier. Yorke, Matthews, and Malins Smith have found a considerable percentage of carriers among lunatics, army recruits, and the personnel of the navy in England. The two former investigators record a figure of 5 per cent., the latter one as high as 19 per cent.; Kuenen has recorded a considerable number of indigenous infections with this parasite in Holland, and Brug estimates the carrier-rate as 12·7 per cent. in that country. In the United States the carrier-rate amongst schoolchildren may be as high as 10·8 per cent., but in adults Andrews and Paulson give a much lower figure, 0·2 per cent. In New York City it is 1·1 per cent. among city dwellers, and 5·4 per cent. among food-handlers, and in a Philadelphia suburb 5·2 per cent. for the general population. The exact significance of these figures is difficult to determine; they certainly do not mean that this comparatively large number of people are suffering from gross ulceration of the bowel, for we know that indigenous *amœbic dysentery* is almost unknown in England. Even among the insane, with a relatively high cyst-passer percentage, "clinical amœbic dysentery" is very

Pathology.—The earliest lesions of amœbic dysentery consist of minute yellow hemispherical elevations of the mucosa, which mark the site of a deeper-lying zone of necrosis. By growing in size and breaking down they form flask-shaped ulcers, the bases of which lie in the submucosa. These ulcers are scattered throughout the large intestine, and rarely extend above the ileo-cæcal valve.[1] The appendix may be involved, and Musgrave, in 1910, reported three cases of fatal peritonitis due to this accident; since then a few other cases have been investigated in which the entamœbæ were demonstrated in microscopic sections of the appendix. Amœbic ulceration of the ileum has been reported by Biggam. They were acute and rapidly fatal cases, and in neither instances were amœbæ found in the stools but only by scraping the amœbic lesions.

The ulcers may not be larger than a pin's head or may enlarge to an inch or more in diameter, and, as the disease progresses, may become even more extensive. In this case the margins are rolled, the edges undermined, and the base is generally formed by the fibres of the muscular coat (sea-anemone ulcers). The ulcers themselves are usually capped by yellowish, greenish, or even black sloughs (Dyak-hair sloughs), which may be of considerable thickness and may project into the lumen of the bowel. The lesions, as a rule, originate in the cæcum, and are scattered throughout the transverse and sigmoid colon and rectal canal, though the intervening mucous membrane remains healthy. As a general rule, amœbic lesions extend throughout the large intestine as far down as the internal anal sphincter. When the process is chronic there is a considerable inflammation and compensatory hypertrophy of the bowel-wall. Often there may be sacculations and constrictions due to the cicatricial contractions of one part of the intestine and attenuation of the other (Plate XIII, Fig. 1).

Sellards and Leiva have shown in experimental animals that when the cæcum is exposed and infective material is introduced into the lumen of the bowel, infection takes place with surprising regularity, but that, whether introduced into the cæcum or *via* the rectum, the initial lesions occur in the extreme lower part of the bowel. Stasis occurring in the large intestine affords an opportunity for the organisms to gain a foothold, and is certainly a factor in determining the location of the initial lesion. Wagner and Beiling, whose conclusions are almost identical with the above, find that the amœbæ at these focal points enter the tissues in one of three ways, passing directly into the connective tissue, into the crypts, or into the lymph-channels, where they migrate to the lymph-follicles and the submucosa. The intestinal mucosa responds to the invasion by the secretion of mucus, which, when mixed with blood, forms an excellent medium for the development of amœbæ on the surface of the mucosa.

Thrombosis of the blood-vessels, in which the entamœbæ are often

[1] The reported discovery of *E. histolytica* in the duodenal juice and bile-passages requires confirmation (Boyers).

found, occurs at the bases of the ulcers, and often, by a process of erosion, an arteriole may be opened, and severe or fatal hæmorrhage result. Perforation by ulcers and even massive gangrene of the gut may occur, especially in the neighbourhood of the cæcum, and lead to fatal peritonitis.

In the healed or healing gut, cicatricial pigmented scars mark the sites of the ulcers. Adhesions may form between proximal coils of intestine ; these may be matted together or become adherent to the liver and spleen. The intestines themselves are very friable and tear readily when handled, so that pericolic abscesses may form.

In chronic cases, polypoid and, it may be, gangrenous tags hang into the lumen of the gut. The intestinal contents may be composed of dark, almost black hæmorrhagic fæcal matter with characteristic penetrating odour.

Carcinoma has been observed to originate at the site of chronic unhealed amœbic lesions.

The cadaver shows no signs of toxic absorption, such as occurs in the bacillary disease. Apart from wasting, the other viscera exhibit few, if any, changes.

Histology.—It is thought that the amœbæ work their way down the crypts of Lieberkühn, multiply, and, by means of a cytolysin, disintegrate the tissues of the submucosa and produce a gelatinous necrosis, with little surrounding tissue reaction (Fig. 59). In more advanced lesions the entamœbæ may be seen lying between the muscular fibres and within the lumina of the peritoneal veins, whence they may be swept as emboli into the portal vein, and lodge in the liver, so becoming the starting-point, either of an amœbic hepatitis or of a liver abscess.

The superficial layers of the slough become secondarily invaded by bacteria, though the adjacent mucous membrane remains healthy and shows few microscopic changes.

Symptoms.—The *incubation period*[1] of amœbic dysentery in man, from the time of introduction of the cysts into the intestinal canal until the development of symptoms, is estimated to be of considerable length. In the Chicago outbreak of 1933 the incubation period ranged from seven up to seventy-seven days, symptoms appearing occasionally within one week and, in a few instances, not for three or four months. The fact that amœbic cysts are found in the fæces of individuals who may never have had "dysentery" in the ordinary accepted sense, apparently suggests that the disease depends upon some secondary condition, the supervention of which is the ultimate determining factor of the explosion of the active disease (*see* p. 525).

[1] The course of experimentally-produced amœbic dysentery in kittens differs essentially from the disease as seen in man. When introduced into the rectum of the cat the entamœba produces within a period of two to three days the most acute inflammation of that part of the intestinal canal to which it has gained access. The lesions differ essentially in their generalized and acute character from those observed in man, and death takes place from a secondary terminal bacterial invasion. Cysts are never formed, and chronic ulceration does not occur.

The great majority of cases of amœbic dysentery run a chronic course, with frequent intermissions and relapses. In fact, the capacity for latency is one of the most striking and characteristic features of amœbic dysentery. The *onset* is generally insidious, and the patient may complain more of diarrhœa than of dysenteric symptoms, and this cannot be too much emphasized. Perforation of the bowel, leading to fatal peritonitis, has been known to occur in patients who

Fig. 59.—Section through base of amœbic ulcer, showing *E. hystolytica* in the tissues. (*C. M. Wenyon.*)

judged by clinical data, were not thought to be suffering from dysentery at all. In mild cases the patient generally complains of suddenly developed attacks of diarrhœa; these may best be described as examples of "*amœbic diarrhœa.*"

The symptoms, both subjective and objective, are rather similar to those of bacillary dysentery; but as a rule the abdominal tenderness is much less acute, and has a definite distribution over the cæcum, where it may simulate appendicitis, and over the transverse colon, where it may resemble gastric ulcer, but more frequently it is limited to the sigmoid colon. Should ulceration occur in the rectum, tenesmus

and straining may be noted. The stools are larger in amount than those of bacillary dysentery. They may not number more than three or four in the twenty-four hours, and they seldom exceed twelve. As a rule, they contain much dark and altered blood, which imparts a penetrating and fetid odour; in consistence and appearance they have been compared to *anchovy sauce*. When mucus is passed, it is streaked with blood and occurs as flecks scattered throughout the faecal mass. Melæna may occur occasionally, the motions may be formed, and streaked with blood and mucus. Gangrenous sloughs may be voided, and even gangrene of the bowel-wall has been recorded. Unless the case is complicated by hepatitis, when the liver is painful and definitely enlarged, there are seldom any toxic manifestations. *Acute* cases of amœbic dysentery with urgent painful and severe clinical manifestations are extremely rare. The Editor has only encountered three which could be classified as such, and this appears to have been the experience of other observers. In the Chicago epidemic, however, acute cases of unusual severity, with pyrexia and toxic manifestations, were noted.

The patient, as a rule, becomes progressively emaciated, but some remain in remarkably good condition, although suffering from repeated relapses, and the Editor has seen patients, suffering from clinical amœbic dysentery, become actually obese. The tongue is moist and coated, vomiting may sometimes occur, and generally there is a complete loss of appetite. Dysuria is not noted as in bacillary dysentery, and *tenesmus* is rare. The *liver* is sometimes slightly enlarged.

As a general rule, in uncomplicated amœbic dysentery there is no pyrexia; irregular fever sometimes observed is due to septic absorption from the bowel. Cases with periodic rigors, suggestive of malaria, are occasionally met with and may be recognized by their amenability to emetine treatment and by the discovery of amœbic cysts in the fæces. In association with amœbic dysentery there is usually a moderate leucocytosis (10,000–12,000 leucocytes with a low proportion of polymorphs—about 70 per cent.).

The study of the clinical manifestations of amœbic dysentery is an extensive subject and there still remain a number of obscure conditions about which some mention must be made. It is probably a true statement to make that, so variable are the symptoms elicited, it may simulate almost any intestinal condition. Intestinal amœbiasis is not *always associated with dysentery or diarrhœa*; it may occasionally be marked by obstinate constipation and by the association of intestinal pains or disturbances very often with neurasthenia, with bodily and mental lassitude, furred tongue, and disordered digestion, what is popularly described as the "uncomfortable belly," or "growling abdomen." In these cases discovery of amœbic cysts in the fæces followed by appropriate treatment may greatly improve the clinical condition. Pathological changes in the bowel, as a result of amœbic infection, may sometimes lead to sacculation, and even to dilatation of

the colon. Very often the cæcum is specially affected, and may become grossly distended with gas and the source of much discomfort.

In the course of chronic amœbic infection a condition of cachexia is produced resembling intestinal toxæmia. The patient has a muddy yellowish complexion and complains of inability to concentrate, and of becoming easily fatigued, resembling very much in outward appearances some cases of diverticulosis.

Often, without treatment, the condition may subside, and the patient may be apparently cured, only to relapse after an interval of weeks, months, or it may be of seven years or even longer. More often the patient continues to pass loose, semi-formed stools, attacks of diarrhœa alternating with constipation. After any physical exhaustion, chill, alcoholic or dietetic indiscretion, a fresh exacerbation may supervene. On account of the variable nature of the symptoms, the shifting character of the pain, and the occasional appearance of melænic stools, it is clear that the condition has to be differentiated from duodenal ulcer, gall-bladder disease, pancreatitis, and intestinal neoplasm.

Hepatitis.—Acute amœbic hepatitis may supervene at any time during the course of amœbic infection: it may come on while the symptoms are acute, or during a remission. The patient usually complains of great pain over the hepatic area, together with symptoms of toxæmia and considerable pyrexia. The liver itself is enlarged; the lower border may project below the coastal margin to the level of the iliac crests, and be extremely tender. Pain referred to the right shoulder is also frequently present. Usually there is a considerable leucocytosis of twenty to thirty thousand.

Such a condition may subside without any active treatment. There is a good deal of evidence that in these cases the amœbæ lie actually within the liver substance, with embolic spread characteristic of a portal distribution. Fortunately this condition is readily amenable to emetine treatment (*see* p. 538).

Complications.—Death may result from exhaustion, intestinal hæmorrhage, perforation, or liver abscess.

Perforation may be sudden, or preceded by intense local pain, which, if confined to the right iliac fossa, may be mistaken for appendicitis. Occasionally, also, a pericolic abscess, especially in the descending or sigmoid colon, may be produced.

The most frequent complication of amœbic dysentery is liver abscess.

Amœbiasis may be superimposed upon an attack of bacillary dysentery, or *vice versa*. In Egypt intestinal amœbiasis is often found in association with *Bilharzia mansoni*. Visceroptosis, distension and sacculation of the gut, leading to intractable intestinal stasis, constitute some of the most distressing sequelæ of amœbic dysentery, but surgical stricture of the bowel is no longer recognized as a complication. *Appendicitis* due to amœbic ulceration is not uncommon.

Sequelæ.—Many sequelæ of intestinal amœbiasis have been

described, often on insufficient evidence, and it is of course very difficult to prove the actual direct association of different obscure clinical states with a past infection with *E. histolytica*. The Editor can record here his impression that certain intestinal conditions occur frequently as an aftermath of *amœbiasis;* such are certainly appendicitis (not necessarily caused by amœbic ulceration), "mucous colitis," and *duodenal ulceration*. Chronic amœbiasis, besides producing a condition of chronic ill-health, very often also brings about introspection and the patient is apt to become a confirmed neurasthenic.

Diagnosis.—Generally it is safe to regard an acutely developing tropical diarrhœa as being of bacillary or of amœbic origin. Clinical distinctions in the less acute forms, taken by themselves, are often unreliable. Assistance may be obtained from the more rapid onset, the febrile condition, and the rapid pulse in the bacillary disease. As a rule the number of stools in bacillary dysentery is greater and their bulk less. The character of the stools should also be taken into account. Usually they contain more dark blood, and, occasionally, may be tarry like melæna, almost suggesting duodenal ulceration.

In these circumstances laboratory diagnosis should be resorted to, the clinician having regard to the experience of the observer and his ability to determine whether any amœba-like body discovered in the fæces be *E. histolytica*, *E. coli*, or merely a large tissue cell, especially a macrophage (Plate XIV). With practice this becomes comparatively easy. Entamœbæ may be absent in some portions of a stool though numerous in others. Several preparations must be searched at first with the $\frac{2}{3}$-in. lens: subsequently with the $\frac{1}{6}$-in., and, whenever possible, a portion of mucus must be picked out for examination. The organisms may be difficult, or almost impossible, to detect in a specimen containing much blood, and it is important that it should be as fresh as possible. This discovery of an active amœba containing ingested red blood-corpuscles is generally sufficient to clinch a diagnosis of *E. histolytica*. In the more chronic and latent forms of the disease the characteristic cysts must be searched for. As has been pointed out many times, entamœbæ and their cysts can at first be recognized under a low-power as "bright stars," being of higher refractility than other body cells. No examination should be considered as completely excluding an amœbic infection until the stool has been searched on *each of seven* consecutive days. The cultural method may assist diagnosis in scanty infections. In all microscopic examinations of the fæces the amœbæ tend to congregate into masses or clumps, so that they may be found in one field and not in another.

In cases in which there is any doubt as to the identity of the cysts,[1] staining, by the rapid or by the more prolonged iron-hæmatoxylin method, may be resorted to (p. 1035). Much valuable information can be obtained by mixing the fresh fæces with a solution of Weigert's iodine (p. 1035), which brings out their nuclei and other characteristics.

[1] Concentration may also be employed for recognition of *E. histolytica* cysts (p. 1035).

Thomson and Robertson stated that Charcot-Leyden crystals are commonly found in the fæces in amœbic dysentery, and they regard their presence in this situation as being of considerable diagnostic importance. These crystals vary very much in size, averaging 5–25 μ; their typical shape resembles that of a whetstone, and they are soluble in warm water, strong mineral acids, and alcohol. They may also be found in preparations made from amœbic ulcers obtained through the sigmoidoscope (Plate XV).

The Editor would emphasize the danger of placing too much stress on the presence of Charcot-Leyden crystals as necessarily diagnostic of intestinal amœbiasis. He has encountered these crystals in association with malignant disease of the rectum, with mucous colitis, with coccidiosis (*Isospora hominis*), ulcerative colitis, and various helminthic infections.

An additional feature which may occasionally serve as a means of differentiation from bacillary dysentery is the moderate leucocytosis of 10,000–15,000, with a low proportion of polymorphonuclear cells, which usually accompanies intestinal amœbiasis.

Complement-fixation reaction (Craig).—Craig has described a technique for the preparation of amœbic antigen and the exact technique for carrying out the test, which is practically the same as that used for the Wassermann reaction. The antigen is an alcoholic extract of cultures of *E. histolytica* grown upon a modified Boeck-Drbohlav medium. A rich culture is selected and from this at least 120 subcultures are made. Then all the material at the junction of the egg slant and Locke's serum solution is pipetted into suitable centrifuge tubes, centrifuged and the sediment extracted in the incubator at 37° C. for fifteen days, with seven and a half volumes of absolute alcohol. Craig has now published results obtained from 1,000 cases in which diagnosis was checked by the fæces examination. Of those giving a positive reaction (175 persons), *E. histolytica* or cysts were found in the fæces of 89·7 per cent.

More recently Meleney and Frye have tested the value of complement-fixation in experimentally infected animals inoculated parenterally with amœbic extracts. Experimentally infected dogs invariably give a positive reaction, but this is not the case in naturally and experimentally infected monkeys, owing to failure of the amœbæ to enter the tissues of these animals.

Sigmoidoscopic examination.—Amœbic ulceration may extend into the rectal canal, so that a sigmoidoscopic examination, which may be conducted without an anæsthetic, may afford valuable information. As a general rule, small yellow ulcers with surrounding hyperæmia are seen; when scraped and examined microscopically it is often possible to find living entamœbæ in the scrapings, even when these organisms cannot be demonstrated in the fæces. As compared with similar examinations in the chronic bacillary disease, the most striking fact is the absence of pain. Amœbic ulcerations may be touched and scraped without causing any sensation to the patient. The mucous membrane surrounding individual lesions shows absence of inflammation, and preserves its normal pinkish colour, but is usually more

reticulated and folded than in a normal subject. Amœbic lesions are then seen in the crypts between the folds ; early lesions may appear either as small, yellow elevations the size of a pin's head, or as superficial snail-track ulcers with hæmorrhagic margins (Plate XVI). Often, again, the only signs of abnormality are small, flame-shaped hæmorrhages, in the centre of which the entamœbæ may be discovered in scrapings obtained by means of long-handled Volkmann's spoon passed through the sigmoidoscope, even, occasionally, when these organisms cannot be demonstrated in the fæces (Fig

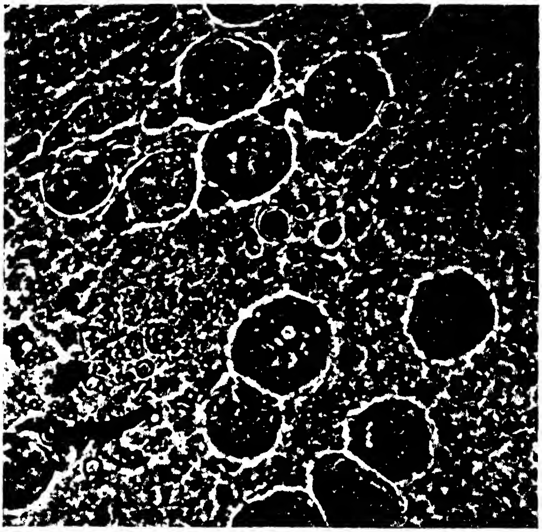


Fig. 60.—Amœbic dysentery, showing tissue-invading *E. histolytica* in scrapings of ulcer obtained through the sigmoidoscope (*Orig.*)

In chronic, partially-healed latent amœbic dysentery, or even in symptomless cyst-passers, amœbic lesions may be distinguished as minute oval circular pits, or depressions, on the mucous surface. They may be almost microscopic in size, requiring a magnifying eyepiece for their detection. The Editor has occasionally found large solitary amœbic ulcers in the rectum, closely resembling carcinoma, which may form as long as twenty years from the time of the primary infection.

Intradermal tests.—Various attempts have been made to elaborate an intradermal test such as that of Scalas. The test material was obtained by mixing mucus containing *E. histolytica* with 30 c.c. of physiological saline solution, and incubating the result for one week at 37° C. with daily shakings and decolorization with animal charcoal.

In positive reactions an indurated swelling at the site of inoculation was obtained.

X-rays in diagnosis.—Vallerino has described filling defects in cæcum and ascending colon with deficient haustration of the bowel, which are indicative of amœbic lesions, subsequent to a barium meal, but not so easily observed after an opaque enema. X-ray diagnosis has been tried out on an extended scale at the Hospital for Tropical Diseases, London. Occasionally filling defects are observed in the cæcum, but similar appearances are seen in other forms of dysentery and colitis. It is disappointing to record that only unsatisfactory assistance can be obtained by this method.

Differential diagnosis.—The differential diagnosis has to be made from many other conditions in which blood and mucus is passed in the stools, and this means, of course, differential diagnosis from all other forms of dysentery, colitis, and even other forms of intestinal disease. There is one aspect, namely, the differential diagnosis from malignant disease of the bowel, which deserves emphasis. Many observers—James, Willmore, Gunn, and Howard—have described a hypertrophic form of intestinal amœbiasis—an amœbic granuloma which may affect different portions of the large bowel, cæcum, or sigmoid, for instance, and which may produce tumours 12 by 10 cm. in extent, and on account of these physical characters may resemble carcinoma very closely. The process consists of an isolated ulcer, with progressive erosion of the bowel-wall in response to long-continued secondary infection. Large amounts of œdematous granulation tissue appear, and the process may affect the entire bowel-wall and the neighbouring mesocolic fat. A satisfactory diagnosis can usually be made by microscopic examinations of scrapings or by removing tissues by biopsy for microscopic section. This also applies to the solitary ulcers described on p. 535.

TREATMENT

So many diverse and different drugs have been advocated in amœbic dysentery that the mental attitude of the practitioner is apt to be confused. The procedure adopted is to name the drugs of importance in logical sequence. While paying due attention to the view of other practitioners, the Editor must express his personal opinion on the value of these various treatments. He prefers the combined method of emetine and yatren or quinoxyl, from which he has had constantly good and permanent results.

The treatment of amœbic dysentery requires careful supervision. Specific drugs may be preceded by a purge—castor oil is the most appropriate; opium, as a routine measure, should be avoided. The dietary should be carefully regulated and in the acute stages careful nursing is important. As all the drugs used in the treatment of amœbiasis contain toxic principles, especially emetine and its compounds, practitioners are cautioned that a definite diagnosis of amœbiasis must be exactly made before they are exhibited. Unfortunately it has become customary to inject emetine indiscriminately as a diagnostic therapeutic measure in all cases of dysentery, often with bad results.

Ipecacuanha.[1]—It had long been recognized in India and in the East that ipecacuanha root was a valuable drug in chronic dysentery; this was Manson's opinion based upon a wide experience in China. Its use is now a matter of history, though it may sometimes be employed. Food should be interdicted for three hours, and then 10 to 20 drops of laudanum given in a tablespoonful of water, and at the same time a mustard plaster applied to the epigastrium to counteract the emetic effects of the drug; about twenty minutes later, when the patient is under the influence of the laudanum, 20 to 30, and even as much as 60 gr. of ipecacuanha, in pill, bolus, capsule, or suspension in half a wineglassful of water, are administered. The dose of ipecacuanha must be continued daily for at least a week, and this drug is still found useful in the after-treatment of liver abscess and amœbiasis of the lung (*see* p. 564).

I. Emetine.—Ipecacuanha has been superseded by its alkaloid. *emetine*, injected subcutaneously, as advocated first by Rogers. There are four alkaloids of ipecacuanha—emetine, cephæline, psychotrine. and emetamine—whose exact constitution is not yet known; but only the first-named has definite therapeutic properties. Emetine must be given subcutaneously or intramuscularly. It is a toxic drug, especially to children and women, when given *intravenously* and in excessive doses.

The rationale of the action of the ipecacuanha alkaloids on *E. histolytica* cannot yet be regarded as settled.

Dobell has shown that emetine is highly lethal to amœbæ in culture, so that a strength of one in five million is specific. Nossina has shown that the action of emetine is influenced by the acidity or otherwise of the medium. It has a slight action in an acid medium, but the effect increases as the reaction approaches neutrality. At pH 6·8 the emetine kills amœbæ in the strength already stated. Cephæline, on the other hand, is far less effective.

In large doses, more than 1 grain a day, emetine produces toxic symptoms. It may lead to asthenia, cardiac irregularity, emaciation, mental depression, and in rare cases to myositis and even to a neuritis which may affect a particular group of muscles and produce partial paralysis. The Editor has seen the scapulo-humeral group attacked, resembling chronic poliomyelitis. Another curious toxic symptom is the production of diarrhœa which may possibly be considered to be due to the dysentery itself. Emetine therapy is frequently followed by a fine branny desquamation of the skin and an atrophic brittle condition of the nails. Emetine given in enema form (1 : 1000) in doses of 2-3 gr., thereby directly introduced into the bowel, is not generally followed by good results; it is extremely painful and may actually provoke an acute relapse of amœbic dysentery. No adequate explanation of this curious action has been forthcoming.

More serious attention must be paid to the toxic manifestations of emetine when given injudiciously without proper indications for its use. Being a

[1] Brazilian ipecacuanha root (*Cephælis ipecacuanhæ*) is said to be more efficacious than the preparation from New Grenada (*Uragoya granatensis*), as it contains more emetine.

general cytoplasmic poison it is especially toxic when given in bacillary dysentery infections on the mistaken notion that they are amœbic. Apart from its general toxic action on the tissues, it has an especial affinity for the heart. Its action has been shown by Epstein to be direct on the myocardium and the conducting fibres, and may produce ventricular fibrillation. Notice must also be drawn to the effects of ill-conducted emetine injections, especially in debilitated persons. It may then produce a widespread cellulitis, and the Editor has seen two cases where it was so acute and extensive that the patient nearly lost his arm. Localized abscess formation may occur, or a patch of irritative eczema, or even an ulcer, may appear at the site of injection. Often the stiffness and irritation produced by emetine injections is intolerable to the patient. Many of these objections may be obviated by giving it by the intramuscular route. Emetine is especially toxic to young children and is a mental depressant to adults.

On no account should emetine be given hypodermically to patients who are up and about, leading an active life or even taking hard physical exercise. This is too frequently forgotten and permanent cardiac damage is the result.

It is advisable to begin treatment with a course of hypodermic or intramuscular injections of emetine hydrochloride (1 gr. in 1 c.c. of distilled water) daily for ten or twelve days. This alone does not suffice for thorough eradication of the infection from the bowel as the Editor has abundantly shown from the following out of past histories of dysenteric patients; it should be supplemented by the *double iodide of emetine and bismuth* (emetine-bismuth iodide), containing 26 per cent. of the emetine alkaloid. Emetine injections[1] constitute a much more effective amœbicide in *metastati amœbic lesions* (hepatitis, etc.) than in intestinal amœbiasis.

II. Emetine-bismuth iodide was introduced by Du Mez in 1916 and popularized by Dale. It contains 58 per cent. of iodine and 28 per cent. of emetine. The insoluble salts of bismuth are converted into bismuth sulphide after passing the pylorus. It is useful, especially in chronic cases and in persistent passers of *E. histolytica* cysts, and should be given by the mouth. Generally known as E.B.I., it is an insoluble powder, from which the emetine is set free by contact with the intestinal juices. Experience has shown that it passes through the intestinal canal unabsorbed, if compressed into a hard tablet, or if coated with an insoluble substance, such as paraffin, vaseline, resin, keratin, or stearin. It is best made up in powder form in gelatin capsules (*slipules*), or mixed with jam or syrup. The maximum individual dose for an adult is 3 gr. (0·2 grm.) per diem; it should be given for ten to twelve consecutive days. With delicate individuals and with women one should begin with a smaller dose—1 gr.—and gradually increase till 3 gr. is reached. This drug is probably more easily tolerated in temperate climates than in the tropics.

The drug is dispensed as a red powder made by Burroughs Wellcome & Co.; the capsules of gelatin are manufactured by Parke Davis, and by Martindale under the trade term of *Slipules*. No. 5 size capsule will contain

[1] Disagreeable sequelæ following emetine injections may be avoided if the skin is pinched up and the needle inserted *deep subcutaneously*.

1 gr. of E.B.I., while 3 gr. can be accommodated within No. 2 size. If the full dose is given, it is better from the point of view of the patient to take one capsule containing 3 gr. When treatment is commenced with smaller doses the patient becomes gradually accommodated to the drug.

As the result of more mature experience, the Editor is of the opinion that the full dosage of 30–36 gr. formerly advocated is inadvisable and is not followed by better results than when smaller doses are administered; with the *combined method of treatment* which he prefers to any other, it is not necessary to administer more than 19 gr. of E.B.I.

It is important to observe certain precautions in giving the drug. When given at 10 p.m., the last food should be taken at 6 p.m., and nothing, not even a glass of milk, thereafter. The patient should remain at rest; he should endeavour to go to sleep, and any saliva should be wiped from the mouth and not swallowed.

The practitioner should remember that vomiting and diarrhœa are to be expected in the earlier part of the course, and are to be viewed as an indication that the drug is being absorbed. Vomiting, unless excessive, is not to be regarded as a contraindication; if no symptoms of nausea supervene, it is possible that the cachets are not being dissolved and their contents set free. It is necessary that the patient should remain in bed and partake of a liquid or milk diet with one egg and toast.

Excessive vomiting and nausea may be prevented by 10–15 min. of tinct. opii given half an hour previously, or, in some patients, by nepenthe, luminal, 1 gr., allonal, or chloretone. Most patients lose about 5 lb. in weight while under treatment. The condition of the heart and pulse should be noted daily, but the treatment should not be discontinued unless depression becomes severe. There is almost invariably a drop in blood-pressure of about 20 mm. of mercury. Alcohol in any form should be prohibited. When the cure is completed the patient should be gradually permitted to resume an active existence, but dieting (*see* p. 544) is still necessary. The results of E.B.I. treatment are much more permanent than those of treatment by injections of emetine. In the Editor's experience most cases treated by emetine-injection, without adjuvant treatment, ultimately suffer from relapses.

For relapsing cases it was formerly thought necessary to give more than one course of E.B.I. treatment, and cases were encountered shortly after the War which were considered to be due to amœbæ which had become resistant to emetine. The Editor is insistent that repeated courses of E.B.I. are harmful to the patient and are not a sound therapeutic procedure. It was also considered necessary to control the course of treatment by frequent and repeated fæcal examinations. Too much reliance should not be paid on isolated fæces examinations on account of the vicarious appearances of the cysts, but it is advisable to examine the fæces microscopically at the end of six weeks after treatment. The results are much better controlled by periodic sigmoidoscopic examinations, if these can be carried out without too great a discomfort to the patient. For some time after the disappearance

of the active lesions, small pits or depressions of the mucous membrane may be seen.

A modification of E.B.I., known as emetine periodide (E.P.I.), is less toxic. It may be given in capsules in the total dosage of 3 gr. daily, in conjunction with capsules of dried ox-bile, gr. 5, taken simultaneously, and this is said to facilitate the liberation of emetine. The Editor is in the habit of administering E.P.I. to those who cannot tolerate E.B.I. He has found the dosage of 6 gr. E.P.I., as advocated by Willmore, too large.

Auremetine (Willmore and Martindale) is a compound of emetine with auramine (a dye). It is given by the mouth in the form of a dark-maroon powder which is insoluble in water. The dose, 1 gr. in gelatin capsules (slipules), is given four times daily on alternate days for seven days, and then daily till a total of 40–60 gr. is taken. In the Editor's experience it is a very depressing drug and causes as much nausea and vomiting as E.B.I., over which it possesses no special advantages.

III. Iodine-oxyquinoline-sulphonic-acid preparations.

(*Yatren*) (*Bayer*).—The drug sodium-iodoxy-quinoline sulphonate is known as *Chiniofon* (Brit. Pharmacopœia), *Quinoxyl* (Burroughs Wellcome), *Quiniosulphan* (May & Baker). Other preparations with similar chemical composition are known as *Anayodin* (U.S.A.)[1] and *Dysentulin* (Germany). It is a mixture prepared from approximately four parts of a 7-iodo-8-hydroxy-quinoline-5-sulphonic acid, containing not less than 26·5 per cent. combined iodine and 1 part of sodium bicarbonate. There is generally some chemical reaction, so that the preparation may contain a small amount of sodium hydroxyquinoline sulphonate in addition to the sodium bicarbonate and iodohydroxy-quinoline sulphonic acid. On dissolving yatren, 100 parts yield approximately 85 parts of iodohydroxyquinoline sulphonate. It can be given by the mouth or by retention enema. The maximum daily dose is 1 grm. (15 gr.) in powder form, in capsules, or keratin-coated pills, for ten days; after an interval of one week the course should be repeated. The drug is excreted in the urine, and can be recognized by the oxyquinoline test (green colour with perchloride of iron). Yatren in pill form, known as yatren pills (4 gr. each), act best when the acute symptoms have been controlled by emetine and in conjunction with that drug. The maximum dose of these is four a day.

In the Editor's opinion, in order to obtain permanent results, yatren must be given by the rectum in the form of a rectal injection (retention enema), as well as by the mouth. By this method yatren has distinct amœbicidal action. The bowel must first be washed out and cleared of mucus by means of an enema (1 pint) of 2-per-cent. sodium bicarbonate. This is best given at 8 a.m. One hour later 227 c.c. (8 oz.) of a 2·5-per-cent. solution of yatren, or quinoxyl, in warm water, is introduced through a stout rectal tube. The patient should be encouraged to retain the solution as long as possible, which he is usually able to do for 8–10 hours. The solution is then excreted per

[1] A somewhat similar compound is iodochlorcxyquinoline or vioform, which has proved itself effective in monkey amœbiasis (Leake).

rectum as a greenish liquid containing mucus and débris derived from the bowel. The course of injections is continued, when well tolerated, for ten days. Sometimes a longer period may be necessary, or the course may even be repeated two or three times with a week's interval between each. Strict dieting and rest in bed are absolutely necessary. Yatren "retention" enemata may be given in 5- or even 10-per-cent. solution to specially intractable cases, but are liable to give rise to pain and discomfort.

IV. Combined treatment.—In the Editor's opinion this method of treatment gives far the best and most permanent results. He has tested it out now in over 600 cases of proven intestinal amœbiasis, and has had two relapses, one of which has subsequently yielded to further treatment. This treatment really embodies the effects of both yatren and E.B.I. treatments given in combination—*not* on alternate days. It is essential that the yatren, or quinoxyl, enema should be retained and that it should not be used as a cleansing enema, as is frequently done. In the Editor's opinion E.B.I. acts on the amœbic lesions in the upper part of the large intestine, and the yatren on those ulcers and lesions situated in the lower portion. It is necessary that the patient should be *at rest* and *in bed* the whole of the ten days during which this treatment is exhibited. Due attention must be paid to the dietary. It is not necessary to give more than 19 gr. of E.B.I. altogether, and the maximum individual dose need not exceed 2 gr.

SCHEME OF DIETARY AND COMBINED TREATMENT FOR INTESTINAL AMŒBIASIS

On waking, potassium-chlorate mouth-wash.
7 a.m., pot of tea and 2 oz. milk.
7.30 a.m., one egg, buttered toast, cup of tea and 2 oz. milk.
8 a.m., sodium-bicarbonate enema 2 per cent. 1 pint.
8.30 a.m., yatren $2\frac{1}{2}$ per cent. by rectum (8 oz.).
9 a.m., 8 oz. milk.
10.30 a.m., juice of an orange, glucose $\frac{1}{2}$ oz.
12 noon, liver soup, chicken or fish (boiled or fried), white sauce, toast, butter, custard or milk jelly, baked apple.
4 p.m., boiled egg, toast, butter, juice of one orange and $\frac{1}{2}$ oz. glucose, or grapes or ripe banana, sponge fingers.
5 p.m., yatren enema voided.
6 p.m., milk 8 oz.; bath.
9.30 p.m., sedative (luminal gr. 1).
10 p.m., E.B.I.
10.30 p.m., sleep.
2 a.m., vomit (therapeutic action of E.B.I.).

During the combined treatment the patient should be nursed in bed and should be allowed to get up for his bath. He may be allowed to use a night commode for stools and for voiding the residue of the yatren enema. On the first night E.B.I., gr. 1, is given, on the second and subsequent nights, gr. 2.

After the completion of the treatment, the patient must be permitted two days' rest in order to regain his strength, as, almost invariably, a sense of weakness or stiffness is produced in the limbs; but if carefully carried out, this treatment is not specially exhausting.

Medicinal treatment following the combined course.—As an after-treatment to the above the Editor is in the habit of prescribing an after-course of yatren (quinoxyl) pills, one or two at night for the next three weeks, according to the age and condition of the patient. These pills are good aperients and probably act by keeping the bowels relaxed. If the patient is much debilitated, one tablet of stovarsol should be given daily for 14 days.

Other methods of treatment.—*Stovarsol* (*Acetarsol*), an arsenical preparation (3-acetylamino-4-hydroxyphenyl-arsonic acid), containing 27·2 per cent. of arsenic, has been advocated, mainly in France, as an amœbicide, and has been widely used in the treatment of amœbic dysentery in combination with other drugs. In the Editor's opinion it has only a feeble amœbicidal action, but it possesses stimulating properties. Its special use is in the after-cure of amœbiasis. It is put up in 4-gr. tablets, and the maximum dose is two daily for one week to ten days, but not longer; in susceptible cases not more than one tablet daily is advisable. The exhibition of this drug has to be carefully watched, as it may give rise to a toxic erythema with pyrexia closely resembling German measles, and even to exfoliative dermatitis which may be fatal. None of these arsenical drugs should be administered to patients in whom toxic spoiling of the liver is suspected. A delayed papular toxic rash may appear three weeks or so after the administration of the drug. Other varieties of this preparation are known as *Spirocid*, *Orarsan* (Boots) and *Acetarsol* (U.S.A.). *Halarsol* (May & Baker) is similar.

Carbarsone (Eli, Lilly & Co.), 4-carbamino-phenyl arsonic acid, ($H_2O_3AsC_6H_4$ $NHCONH_2$), was originally prepared by Ehrlich and contains 28·8 per cent. of arsenic. It has been much used in America and is given in the same manner as stovarsol, and has apparently the same properties. On account of its arsenical content it should not be given in hepatic complications. Most American authorities advise a dose of 0·25 grm. twice daily in capsules (pulvules) for ten days. Both stovarsol and carbarsone may be administered per rectum in the form of retention enema of 2 grm. in 200 c.c. of warm 2-per-cent. sodium bicarbonate solution. *Amibiarson* is also a compound similar to the above. These compounds are useful in cyst-passer cases.

Kurchi and derivatives.—(*a*) Kurchi *bark* (containing an alkaloid, *conessine*) was given a few years ago, in 10-gr. tablets three times daily for a lengthy period, as an after-treatment in intractable cases. It apparently has no special action. (*b*) *Kurchinine hydrochloride* (Whiffen & Sons Ltd.), a crystalline alkaloid from kurchi bark, has been used both for oral administration and hypodermic injections

in doses of ½–1 gr. on three successive days. This has been succeeded by *Kurchi bismuthous iodide* (*Anabin*) which contains the total alkaloids of the bark. According to Acton and Chopra it is given by the mouth in 10-gr. doses, twice daily for ten days without producing any deleterious effects. Although the first reports of the treatment were encouraging, the later after-effects, in the Editor's experience, have been disappointing.

Ko-sam is dispensed in tabloid form by Burroughs Wellcome and is prepared from the seeds of *Brucea sumatrana ;* it has a reputation for the cure of amœbiasis in the Far East.

Rivanol, a derivative of acridine, injected per rectum, appears to have a somewhat similar action to yatren. A preliminary cleansing, non-irritating enema is given and rivanol in distilled water is diluted 1 : 500 to 1 : 2000 ; of this 500–800 c.c. at body-temperature is administered per rectum with the patient lying on his side, or in the knee-elbow position. The injection must be retained as long as possible, at least fifteen minutes. A course of ten or more treatments is necessary. Rivanol is antispasmodic and antiseptic and is useful for the relief of pain and tenesmus, especially in that distressing disease, ulcerative colitis. Peter advocates it in tablets (Rivanolettes) by the mouth, 30–50 mg. three times daily for nine days.

Vioform, or enterovioform (iodochlorhydroxyquinoline), has been employed in place of iodoform and contains 37·5 per cent. of iodine. It is given by the mouth in gelatin capsules, each containing 0·25 grm. (4 gr.) of the powder, three times daily for ten days. In chronic cases it may be given each night for ten days in the form of a retention enema, each consisting of 150–200 c.c. of warm water in which is dissolved 2 tablets.

Bismuth subnitrate.—As an adjuvant to emetine treatment Deeks and James strongly advocated bismuth subnitrate in heroic doses—180 gr. mechanically suspended in a tumblerful of milk or water every three hours, night and day, in severe cases. Occasional untoward effects are noted, such as cyanosis and forcible action of the heart, and they are due to impure bismuth. During the first ten days of this treatment a strict dietary is necessary ; thereafter a non-irritating diet must be persisted in for two or three months.

Treatment of hepatitis.—The possible supervention of amœbic hepatitis with pyrexia and rigors should be borne in mind. During the whole course of an attack of amœbic dysentery, and for months afterwards, the condition of the liver must receive the most careful attention. We may not be able to prevent abscess of this organ ; but if pain seems to suggest it, we can try, by means of repeated doses of emetine by subcutaneous injection, saline aperients, rest, low diet, fomentations, dry-cupping, and similar measures, to avert a very grave complication. Emetine acts much more rapidly and specifically in hepatitis than in amœbic infection of the bowel ; in some cases actual aspiration of the liver (hepatic phlebotomy) has a wonderful effect. Usually 6 gr. of emetine suffice to overcome the more active symptoms.

Perforation of amœbic ulcer.—In order to avoid fatal peritonitis, every effort to diagnose perforation of the large bowel should be made directly rupture has taken place. This is usually very difficult. Two

successful instances, at least, have been recorded where timely operation has saved the patient's life.

Other considerations.—Symptoms must be treated as they arise. Abdominal pain should be counteracted by means of hot applications, colic by means of a belladonna and bromide mixture (*see* p. 518), and tenesmus by morphia suppositories or by a starch-and-opium enema.

Diet.—The question of a suitable diet in the convalescent treatment of amœbic dysentery is an all-important one after the combined yatren (quinoxyl) and E.B.I. treatment, for example ; the precautions advocated are necessary in view of the tendency of this disease to relapse when the patient indulges in rich and highly nitrogenous food, or foods containing too much starch.[1] Alcohol, unless taken in small quantities, certainly predisposes to relapse. The following diet is advocated to be taken for four weeks after active treatment :

Permitted.—Porridge ; eggs ; filleted or fried fish—haddock, plaice, cod, sole or whiting ; toast or rusks ; milk puddings—rice, sago, semolina, ground rice ; spinach or young peas, vegetable marrow, cauliflower ; plain cakes ; fruit jellies ; stewed pears or peaches ; baked apples ; bananas, grapes ; tripe, brains, sweetbreads ; chicken ; rabbit ; game—pheasant, partridge pigeon.

Not permitted.—Cheese ; new bread ; potatoes ; fats ; suet puddings ; rich cakes with raisins or spices ; pastry of all kinds ; pickles.

Beverages.—Light wine only ; no spirits, beer, or stout.

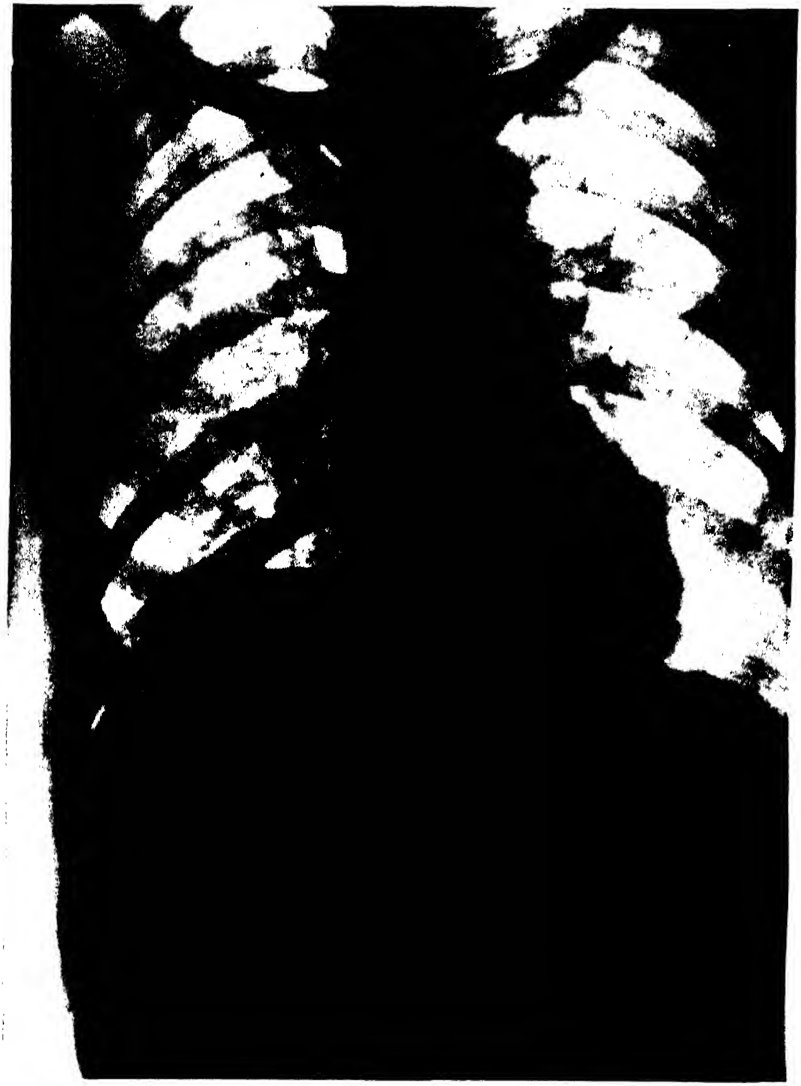
Meat.—Red meat, i.e. mutton or beef, can be permitted with safety once daily.

One should be reasonable in these matters ; it is not necessary to starve one's patients in any way.

Surgical measures must be reserved for the complications of amœbiasis. Such heroic procedures as cæcostomy have no place in the treatment of intestinal amœbiasis.

Prophylaxis of amœbiasis is practically the same as that already described for bacillary dysentery, and depends upon efficient sanitation, measures directed especially against the housefly, which has been proved to be a carrier of the amœbic cysts, and the avoidance in the tropics of unboiled water, raw vegetables, or other foods that may have been contaminated by human fæces. As the cysts of *E. histolytica* can only survive in a moist medium, there is a considerable amount of evidence, experimental and epidemiological, that amœbic infection is mostly water-borne. The problem of dealing with human carriers of *E. histolytica* cysts is one that is engaging the minds of sanitarians at the present time. It is not likely to arise in countries supplied with a proper system of sanitation, but in no case ought a cyst-carrier to be employed as a cook or mess orderly, or placed on water duties. Wherever possible, cyst-carriers should be treated by the combined method with emetine-bismuth-iodide and yatren (quinoxyl), though a prolonged course of carbarsone is sometimes effective.

[1] This statement has some experimental basis. Brumpt has shown that in artificial culture the entamœbæ eagerly ingest starch grains (*see* p. 858).



Radiograph of dome of diaphragm in liver abscess.
(Dr. Carmichael Low.)

LIVER ABSCESS.

PLATE XVII

Radiograph of cretified abscess in right lobe of liver.

(Orig. case. Radiograph by Dr. M. Cordiner.)

LIVER ABSCESS.

PLATE XVIII

Taking yatren, or quinoxyl, in pill or tablet form (4 gr.) at night in tropical countries where amœbiasis is rife appears to serve in some way as a prophylactic measure, as well as acting as a satisfactory aperient.

As amœbiasis is usually a water-borne disease, efforts have been directed to exterminating the amœbic cysts from a contaminated water supply. It has not been found possible to do so by medication of the water by chlorine or chloramine. Spector, Baylis and Gullans have proved that this can best be done by removing the cysts by filtration through sand-filters, combined with coagulation.

Complications of Amœbiasis

1. HEPATIC ABSCESS (LIVER ABSCESS; HEPATIC AMŒBIASIS)

Geographical distribution.—Liver abscess of the type known as tropical abscess, for the most part a disease of warm climates, corresponds in its distribution with amœbic dysentery. While the entamœba is the principal element in its production, its incidence depends probably on the special susceptibility of the European to amœbic infection.

Ætiology. *Relation to amœbic dysentery.*—There can be no question as to the existence of an intimate relationship between amœbic dysentery and liver abscess. Many well-authenticated statistics, as well as everyday experience, attest this. In 3,680 dysentery autopsies made in various tropical countries, and collated by Woodward, 779 (21 per cent.) revealed abscesses of the liver. It will be remembered that extensive amœbic ulceration may exist without exciting any subjective symptoms whatever. Moreover, many patients suffering from liver abscess forget, or fail to mention, the occurrence of a previous dysenteric attack, or may mislead the physician by describing such an attack as "diarrhœa," so that the relationship is much more intimate than even statistics would indicate. In the great majority of cases dysentery antedates the abscess, it may be by twenty years.

Race, sex, and climate.—Though common in Europeans in the tropics, liver abscess is proportionately rare among natives. Thus, in the native army of India the proportion of deaths from liver abscess to the total mortality in 1894 was only 0·6 per cent., whereas in the British army it was 7·4 per cent. Man for man, the relative liability of the European and the native soldier was as 95·2 to 4·8. This disproportion holds, in spite of the fact that a larger proportion of the latter are infected with *E. histolytica*.

It is well known that European women in the tropics, though nearly as subject to dysentery as European men, rarely suffer from liver abscess; children hardly ever. It is most common between the ages of 20 and 40, though with regard to children, there are records of amœbic abscesses of the liver in Egyptian children of three months of age and again of others in children in India of ten years of age. The youngest seen in the Editor's experience was in an English girl of sixteen.

Pathology.—It may be inferred from the symptoms that in the early stages of suppurative hepatitis there is general congestion and enlargement of the liver; in some instances this condition may be more or less confined to one lobe or even part of a lobe. Later, as we know more especially from observations in cases that have died from the attendant dysentery, one or more greyish, ill-defined, circular patches, ½–1 in. or thereabouts in diameter, are formed. These grey spots are very evident on section of the organ. A, drop or two of a reddish, gummy pus may be expressed from the necrotic, patches—for such they are. Still later, the centres liquefy, and distinct but ragged abscess cavities are formed. An abscess thus commenced extends partly by molecular breaking down; partly by more massive necrosis of portions of its wall; partly by the formation of additional foci of softening in the neighbourhood and subsequent breaking down of the intervening septa. The walls have a ragged and tessellated appearance. As the abscess enlarges so the zone of necrotic tissue becomes narrower. The character of

Fig. 61.—Multiple liver-abscesses from a case of acute amœbic dysentery showing characteristic structure and zone of acute hyperæmia. Quarter nat. size. (*Orig.*)

the contained pus also changes during the evolution of the abscess, and it frequently becomes secondarily infected with streptococci and other organisms, when it assumes a brownish or greenish colour.

Number, size, and situation of abscesses.—Liver abscess may be single or multiple. If multiple, there may be two, three, or many of them. When single, the abscess sometimes attains a great size. Frequently it is as large as a coco-nut, or even larger; it has happened that the entire liver, with the exception of a narrow zone of hepatic tissue, has been converted into a huge abscess sac. When multiple, the individual abscesses are generally smaller, ranging from the size of a filbert to that of an orange (Fig. 61).

As might be expected from considerations of the relative size of the parts, single abscess is much more common in the right than in the left and smaller lobe. What might be termed the seat of election is the upper part of the right lobe.

Adhesions to surrounding organs are frequently, though not invariably, formed as the abscess approaches the surface of the liver. In this way the danger of intraperitoneal extravasation is usually averted.

Intestinal ulceration usually coexists; it may be very extensive, or confined to a few small punched-out ulcers, generally in the neighbourhood of the cæcum. Or, again, there may be no visible lesions of the mucous surface at all.

Pulmonary inflammation and abscess from escape of liver pus into the lungs are sometimes discovered post mortem. Generally the pulmonary abscess communicates with the mother abscess in the liver by a small opening in the diaphragm, the pleural sac as a whole being shut off by adhesions.

Liver pus.—The naked-eye appearance of liver pus is peculiar, and almost characteristic. When newly evacuated it is usually chocolate-coloured, and streaked, or mixed, with larger or smaller clots or streaks of blood. and here and there with streaks of clear mucoid or yellowish material. It is so thick and viscid that it will hardly soak into the dressings; it lies on the surface of the gauze like treacle on bread, spreading out between the skin and the dressing, and finding its way past the edge of the latter rather than penetrating it. When quite fresh, here and there little islands of what may be described as laudable pus may be made out in the brown mass. Sometimes it contains considerable pieces of necrotic tissue. Occasionally, from admixture of bile, the abscess contents are green-tinged; they are rarely offensive unless the abscess lies near the colon, in which case it may have a fæcal odour. Under the microscope many blood-corpuscles are discoverable, besides much broken-down liver tissue, large granular pigmented spherical cells, leucocytes, debris, oil globules, hæmatoidin and, occasionally, Charcot-Leyden crystals and entamœbæ; when secondarily infected with organisms. streptococci or *B. coli* are also found.

Entamœbæ and pyogenic organisms.—The experience of tropical abscess in Egypt, India, and elsewhere is that entamœbæ may be detected in half the cases. Usually they cannot be found in freshly aspirated liver pus, or in the matter which escapes during operation, but they appear, often in great profusion, four or five days later in the discharge from the drainage-tube. In these circumstances they may occur in strings of eight or ten. Unless the patient is treated with emetine, the amœbæ may persist in the discharge until the abscess has healed. The Editor has succeeded in growing them from liver-abscess pus on Drbohlav's medium. Their appearance in the pus coming from the walls of the abscess a few days after operation suggests that the habitat of the parasite is not so much the pus occupying the general abscess cavity as that immediately in contact with the wall and the breaking-down tissues themselves. The longer the abscess has persisted the larger its size, and the more difficult it becomes to find amœbæ (Fig. 62). The pus from a large proportion of cases is bacteriologically sterile, but occasionally may become secondarily infected by *Bacillus coli* or hæmolytic streptococci. Cysts of *E. histolytica* are never found.

Encystment.—In rare instances the pus of liver abscess, instead of possessing the chocolate colour and viscid consistence described above, is yellow and creamy. This is particularly the case when the abscess becomes encysted—an occasional event. The walls of these encysted abscesses are thick, smooth, resistant, and fibrous. In time their contents become cheesy, and ultimately cretified; in the latter event the cyst shrivels up and contracts to a small size (*see* Plate XVIII).

Rogers considers that cirrhosis of the liver which is so frequent in India may be a sequel to liver abscess, but there has been no general agreement on this subject.

Note on the bilaterality of the liver.—Until recently it was considered that no differences existed between the right and left branches of the portal vein, the hepatic artery and the hepatic ducts, although the right lobe of the liver is treble the size of the left. Cantlie in 1884 first noted

hypertrophy of the left lobe of the liver consequent upon total destruction of the right. On this account, and also on account of the embryological development of the liver, it was suggested that the present anatomical division of the liver is incorrect and that its symmetry should be gauged, not by the antero-posterior fissure, but by a line drawn from before backwards, through the fundus of the gall-bladder to the spot where the anterior vena cava grooves the back of the liver. This is the mid-line of the liver, and that this

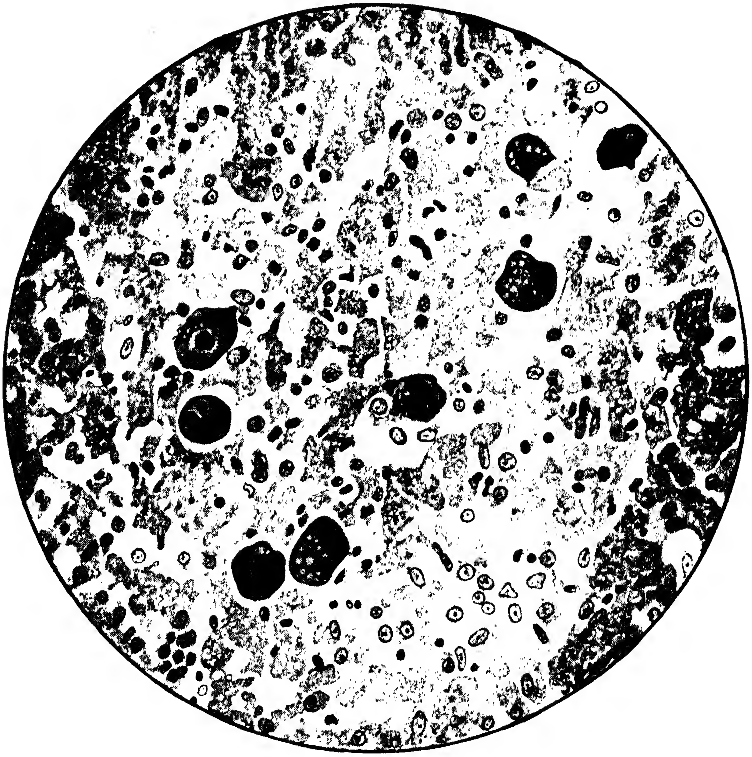


Fig. 62.—Microscopical section of liver abscess, showing *Entamœba histolytica* at margin of abscess cavity surrounded by necrotic liver cells. (*Orig.*)

is the true anatomical division is borne out by pathological studies and injection of the portal and hepatic veins and the hepatic artery (McIndoe and Counseller). Moreover, Copher and Dick (1928) have shown that the distribution of the portal streams in the liver of the dog can be determined by injections of trypanblue, and then they have demonstrated that at least three distinct and separate currents run in the portal vein. This is a streamline phenomenon. The Editor has had experience of a fatal case in which total destruction of the right lobe of the liver had been brought about by multiple liver abscesses, and in consequence hypertrophy of the left lobe had

taken place so that it formed a distinct tumour which could be palpated in the left hyperchondrium.

The genesis of liver abscess.—Amœbic abscess of the liver would appear to take place from portal embolic infection from some amœbic ulcer in the bowel. According to Rogers, the situation of this infective focus is in the right sector of the abdomen, either in the cæcum or ascending colon—and this fact, therefore, taking into consideration the principles enunciated above, accounts for the common situation in the right hepatic lobe. Direct infection of the anterior surface of the liver may possibly sometimes take place from an ulcer in the hepatic flexure, *via* the peritoneum, but there is no evidence to show that this constitutes the usual method. In *amœbic hepatitis*, which is probably the precursor of amœbic abscess, there appears to be a massive portal infection with amœbæ, a portal pyæmia, in fact. It appears probable that the greater majority of these organisms become destroyed by the resulting tissue-reaction; those that survive multiply and cause necrosis of the surrounding liver cells and the starting point of a liver abscess. Cytolysis of the tissue cells is brought about by the action of the rapidly multiplying amœbæ: but there comes a time when the amœbæ themselves are destroyed by the products of their own activity. Sterile amœbic abscesses at this stage are naturally very liable to become secondarily infected with pyogenic organisms, as not infrequently happens. As originally pointed out by Councilman and Lafleur, the primary lesion is a central necrosis of the liver lobule. This may or may not be the prelude to subsequent abscess formation.

Symptoms.—There is a great variety in the symptoms which liver abscess may produce. As a general rule the patient is one who has long resided in the tropics and who may have at some time or other suffered from subacute attacks of dysentery. He becomes conscious of a sense of weight and fullness in the right hypochondrium, and later he suffers from sharp stabbing pains over the hepatic area, and perhaps a dry cough which makes the pain more apparent.

Shoulder pain.—In a considerable proportion of cases a sensation of uneasiness or actual pain, rheumatic in character, is felt around the right shoulder-joint, especially at night-time. Usually the pain and tenderness are felt in the skin around the acromial region (appropriately termed by patients, "the liver wing"). It is reflex in character due to irritation of the phrenic nerve, and is reflected through the fourth cervical root from which the supra-acromial and supra-clavicular cutaneous nerves arise in the cervical plexus, and is of the same nature as in inflammatory conditions of the lung and pleura and caused by diaphragmatic pleurisy and sometimes in gall-bladder disease. In left-lobe abscess the pain is referred to the *left* shoulder-joint.

General features. Soon the patient becomes feverish, particularly

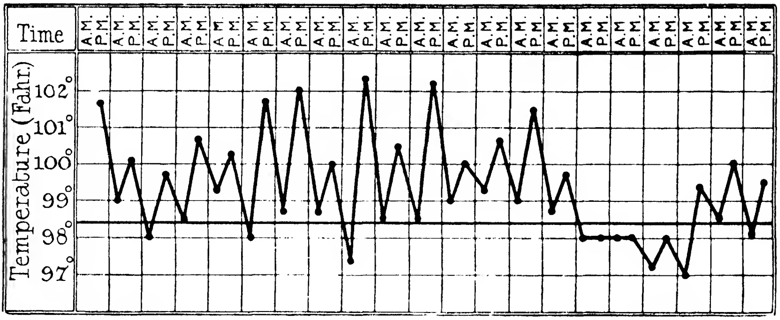


Chart 22.—**Amœbic abscess of liver.** (*Orig.*)

towards the evening, and may experience a few short rigors. He begins to lose flesh, and his complexion assumes a curious yellow, muddy tinge. The quotidian rise of temperature now becomes a regular feature, the thermometer every evening touching 102° F., and sinking to below normal in the morning (Charts 22, 23). The pyrexial bouts are accompanied by most profuse sweats, necessitating frequent changing of clothing during the night. The patient is found to be emaciated, his tongue furred, the extremities cold and clammy; the breath is shallow and mainly thoracic; sometimes an actual fullness in the epigastrium may be observed; con-

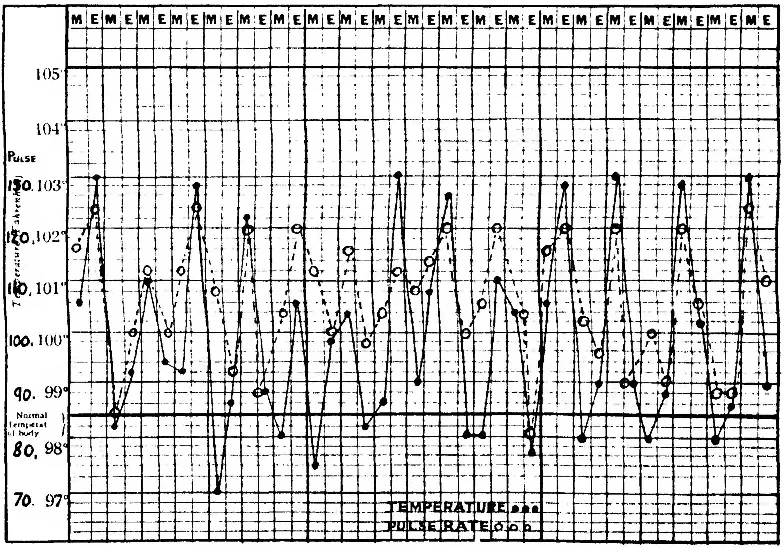


Chart 23.—**Amœbic abscess of liver.** (*Orig.*)

Hectic fever with tendency to tertian periodicity. Dotted line = pulse-rate.

siderable discomfort, and, it may be, deep-seated pain, are produced by general palpation and heavy percussion over the right hypochondrium. In the majority of cases the lower border of the liver is found to be enlarged below the costal margin; sometimes, but less frequently, it extends upwards an inch too high, while posteriorly it can be detected from an angle of the scapula to the costal margin. It may be further observed that the line of dullness is arched along its upper border, and that it is altered by changes of position; the upper line descending when the patient lies on his left side or when he stands up. Deep inspiration may give rise to acute pain, and sometimes one or two tender spots may be discovered in the lower intercostal spaces; the spleen is not enlarged. On auscultation, a pleuritic rub may be detected at the base of the right lung, or signs of compression such as inspiratory crepitations, decreased breath-sounds, and a diminution of vocal fremitus may be noted at the right base (Fig. 63). Pain is usually relieved by lying on the affected side (Figs. 64, 65).

Fig. 63. Clinical picture of liver abscess, showing enlargement of liver and bulging of chest wall. (*Orig.*)

In abscess of the left lobe a tumour of variable outline, sometimes resembling in shape and position that of an enlarged spleen, may be present in the epi- or hypogastrium, and there is usually some involvement of the base of the left lung; but it must always be remembered that a tumour which may be taken for an abscess in the left lobe of the liver may in reality be due to compensatory hypertrophy of the undamaged left lobe.

As the case progresses, the patient becomes more emaciated; hectic fever with drenching nocturnal sweats continues; the liver dullness and pain may increase; or the general enlargement may somewhat subside, and percussion may reveal a local bulging, upwards or downwards. If the abscess which has now formed is not relieved by operation, after months of illness the patient may die worn out; or the abscess, which has attained enormous dimensions, may burst into the right lung or pleura, or elsewhere, and be discharged, and

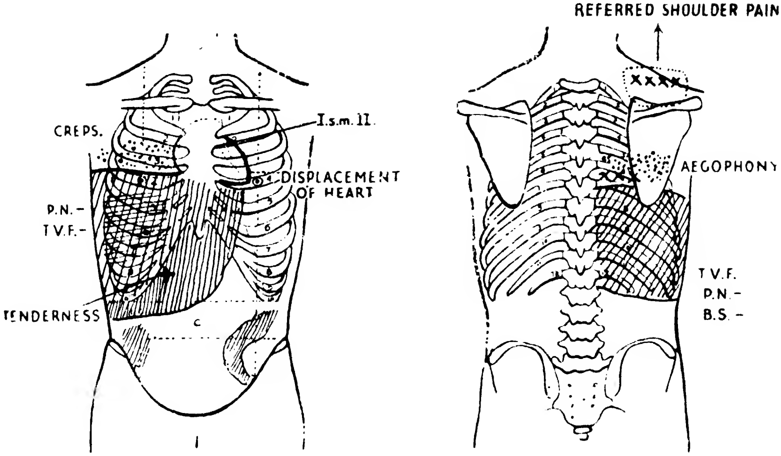


Fig. 64.—Physical signs of liver abscess of right lobe of liver, cured by aspiration with Potain's aspirator (6.7.25). *(Orig.)*

Leucocytes, 9,000 ; *E. histolytica* cysts in fæces. I.s.m. II, basal systolic murmur; P.N. —, percussion note diminished ; T.V.F. —, tactile vocal fremitus diminished ; B.S. —, breath-sounds absent ; CREPS., crepitations.

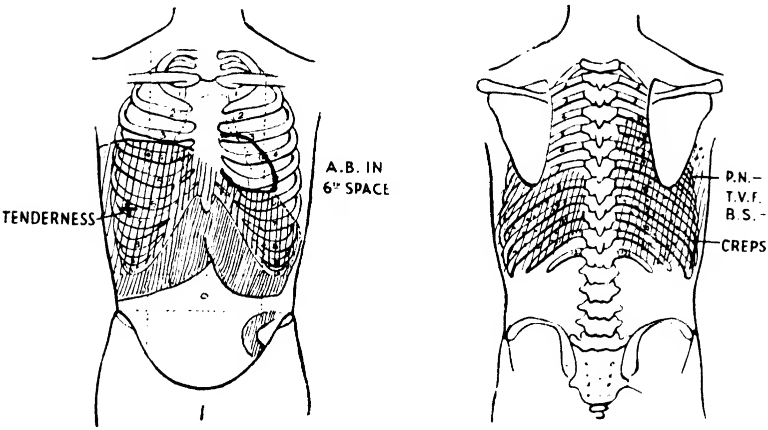


Fig. 65.—Physical signs of liver abscess with hypertrophy of the left lobe, cured by aspiration of 65 ounces of sterile pus (21.12.21). *(Orig.)*

Leucocytes, 12,000 ; *E. histolytica* cysts in fæces. A.B. apex-beat ; P.N. —, percussion note diminished ; T.V.F. —, tactile vocal fremitus diminished B.S. —, breath-sounds absent ; CREPS., crepitations.

either recovery, or death from continued hectic fever and exhaustion or from some intercurrent complication, ensue.

The blood shows a well-marked polymorphonuclear leucocytosis of 15,000–35,000, though in some rare cases no rise of the leucocytes occurs. The mean average of the differential count in the Editor's series of cases is 70·8 per cent. polymorphonuclears; 22·2 per cent. lymphocytes; 6 per cent. large mononuclears; and 1 per cent. eosinophiles. With liver abscess of long duration there is usually a severe secondary anæmia. Very occasionally the blood changes may approximate those of the pernicious type.

Great variety in the urgency of symptoms.—Although the foregoing is a fairly common history in liver abscess, there are many instances in which the initial symptoms are much more urgent and the disease progresses much more rapidly. In other instances subjective symptoms are almost entirely absent, or so subdued that the true nature of the case may be entirely misapprehended until the abscess bursts through the lung or bowel, or a fluctuating tumour appears in the neighbourhood of the liver: or, perhaps, until after death, when the unsuspected abscess is discovered on the post-mortem table.

Sometimes the initial fever is high, and persists for a considerable time, but later it usually becomes distinctly quotidian and intermittent in type; rarely temperatures of 103° and 104° F. may be recorded. There is not one single cardinal sign which may not be absent in hepatic abscess; thus, large collections of pus have been noted unattended by fever of any description. Marked rigors are rare, but when present indicate threatened rupture through the diaphragm or into some viscus. The sweating accompanying the pyrexia usually takes place about the head and neck. Enlarged cervical and axillary glands on the affected side may sometimes occur, while rheumatic-like pains and swellings, which may accompany any chronic infection, may be noted. Pain of some description is rarely absent. A sense of fullness and weight in the region of the liver, which may be referred to the infrascapular region is commonly complained of; stabbing and stitch-like pains may be increased by pressure, and especially by deep inspiration or coughing. Localized painful areas usually occur below the costal margin, and indicate that the abscess is pointing in that direction. Pain on swallowing, at the moment the bolus traverses the lower end of the œsophagus, has been recorded. Pain on firm pressure with the finger-tips in an intercostal space, and over a limited area, is a common and valuable localizing sign. Pain in the shoulder is present in about one-sixth of the cases, and may be the only symptom complained of. It may be noted before the advent of the fever.

Attention may be drawn to the respiratory symptoms; a cough of a painful character, possibly due to reflex irritation of the diaphragm, may be a prominent symptom, while the respiration may be rapid and shallow. The patient usually lies on his back, inclining slightly to the affected side; if the abscess is on the right, lying on the *left*

side becomes distressing owing to adhesions, or possibly to pressure on the heart.

The tongue is generally furred, the digestion disturbed ; flatulence and diarrhœa are frequently noted. There may be concurrent amœbic dysentery with blood and mucus in the stools.

The *area of hepatic dullness* is usually extended upwards and downwards, rarely horizontally. The upper line is not, as a rule, horizontal as in hydrothorax ; usually, on approaching the spine it turns downwards.

The heart may be displaced laterally or upwards by pressure of the abscess when this is of a large size. Tachycardia and cardiac irregularities may result from toxic absorption or from pressure.

Swellings in the epi- or hypogastrium may be noted, simulating closely intra-abdominal tumours, and in apyrexial cases their nature may not be suspected until they are aspirated ; varicosity of the epigastric veins may also be observed. Local *œdema* over one or more intercostal spaces is sometimes apparent ; local *bulging* usually indicates the pointing of the abscess (Fig. 63).

Friction rubs, pleuritic or peritoneal, may sometimes be found ; while pneumonic signs at the right base indicate contiguity of the abscess to the diaphragm.

The abscess may rupture into any contiguous organ, and thereby produce spontaneous cure ; most generally it ruptures into the lung or pleura. When into the *lung*, the abscess contents may be suddenly coughed up in mouthfuls of frothy pus and blood ; generally this process is much more gradual, a few drachms being brought up at a time, but in favourable cases the expectoration gradually diminishes. Amœbic abscess of the lung—often resulting from trans-diaphragmatic rupture—is liable to be mistaken for pulmonary tuberculosis. Amœbæ are not usually found in the expectorated pus, in which striated muscular fibres from the diaphragm may be recognized.

Arrest of the discharge may not mean recovery ; cessation of the cough may be followed by a rise of temperature and reappearance of night-sweats. The alternate emptying and refilling of the abscess cavity may recur many times before recovery finally takes place. In some cases expectoration never ceases, and is accompanied by other signs of pulmonary absorption, such as respiratory distress and clubbed fingers.

A sudden rupture is often accompanied by the passage of melænic stools.

The appearance of the expectorated liver-pus is usually pathognomonic, being chocolate-brown in colour and particularly viscid. When hæmorrhagic, these cases are very apt to be treated as examples of tuberculous hæmoptysis.

Rupture into the *pleura* may lead to a suddenly developed pleural effusion, which may give rise to all the signs of empyema. Aspiration

above the line of the pus in these cases may yield a clear yellow and highly albuminous pleuritic fluid. Pneumothorax may occur.

An hepatic abscess may rupture into the *stomach*, causing vomiting of pus ; into the *bowel*, causing diarrhœa and discharge of pus in the fæces ; or it may burst, with fatal results, into the *pericardium* or *peritoneum*. Pericarditis in association, caused by close contact with the intrahepatic suppuration, has been recorded by Purcell.

Finally, spontaneous rupture may take place through the skin of the abdominal wall, and the abscess thus empty itself in a painless and natural manner. This is the most favourable natural cure of liver abscess. The skin itself may become secondarily infected with amœbæ.

From a study of 50 cases under the Editor's care it has been possible to set out the following table.

	Per cent.
History of previous dysentery	60
Entamœba histolytica or cysts	45
Shoulder pain, right	44
,, ,, left	4·4
Pyrexia, intermittent	77
,, remittent typhoid-like	8
,, sudden onset, rigors	4
Pyrexia absent	13
Night-sweats	82
Dysenteric infiltration of bowel—	
Sigmoid flexure	24
Cæcum and sigmoid	8
Enlargement of liver, upwards	24
,, ,, downwards	75
Pain and tenderness in liver	57
Displacement of heart	8
Associated signs at base of right lung	75
Pleuritic rub	12
Rupture of abscess into lung	11

Mortality.—Formerly the case-mortality was high, 50–80 per cent., but at the present day, owing to the use of ipecacuanha and emetine, and to recognition of the intimate connection of liver abscess with amœbic dysentery, the adoption of improved methods for the evacuation of pus, combined with medicinal treatment, has brought the mortality-rate to practically nothing. Death, when it ensues, may be due to pressure on the abscess, to rupture and gangrene of the abscess-wall, to pneumothorax, to pneumonia, to associated dysentery or other intercurrent disease. Recovery may follow encystment or, possibly, absorption of the abscess.

Diagnosis.—Of all the grave tropical diseases, none is so frequently overlooked as abscess of the liver. Acute sthenic cases are readily enough recognized ; not so the insidious asthenic cases.

The most common mistakes in diagnosis are : (1) Failure to recognize the presence of disease of any description, even when an enormous abscess may occupy the liver. (2) Misinterpretation of the significance and nature of a basal pneumonia—a condition so often accompanying suppurative hepatitis. (3) Attributing the fever symptomatic of liver abscess to malaria. (4) Mistaking other diseases for abscess of the liver, and *vice versa*—for example, hepatitis of a non-suppurative nature, such as that attending malarial attacks ; suppurative hepatitis before the formation of abscess ; syphilitic disease of the liver—softening gummata which are often attended with fever of a hectic type ; pylephlebitis ; suppurating hydatid ; gall-stone and inflammation of the gall-bladder ; subphrenic abscess due to ruptured gastric or duodenal ulcer, or appendix abscess ; abscess of the abdominal or thoracic wall ; pleurisy ; encysted empyema ; pyelitis of the right kidney ; bilharziasis ; scurvy and similar blood-diseases associated with hepatic enlargement ; ulcerative endocarditis ; kala-azar ; undulant fever ; trypanosomiasis, tuberculosis, and malignant disease. Any of these may be attended with fever of a hectic type, increased area of hepatic percussion dullness, and pain in or about the liver.

Differential diagnosis from suppurative cholecystitis without the aid of a " shadowcoll " examination may be particularly difficult.

Cantlie originally classified pus in the neighbourhood of the liver into :

(1) Suprahepatic abscess ;
(2) Intrahepatic abscess ;
(3) Infrahepatic or subhepatic abscess.

Suprahepatic abscess is not synonymous with what is known as " Subdiaphragmatic abscess." By suprahepatic abscess is meant the formation of pus between layers of the broad ligament of the liver.

Frequently a correct diagnosis can be arrived at only by repeated and careful study of the case in all its aspects. Golden rules in tropical practice are to think of hepatic abscess in all cases of progressive deterioration of health ; and to suspect it in all obscure abdominal cases associated with evening rise of temperature and, this particularly if there be an upward enlargement of or pain in the liver, leucocytosis, and a history of dysentery—not necessarily recent.

Low pneumonia of the right base in a tropical patient should always be regarded with suspicion, for it may mean abscess of the subjacent liver.

The presence of *Entamœba histolytica* cysts in the fæces is suggestive, but by no means conclusive, of amœbic abscess. They are found in about 45 per cent. of cases, and amœbæ may occasionally be cultured from the fæces in cases in which they are not visible under the microscope.

An X-ray examination may confirm the upward enlargement in the liver, and bulging of the right dome of the diaphragm, which does not move on respiration (Plate XVII) ; should, however, the abscess

be situated in the centre of the liver, even if it be of considerable size, no definite information is usually obtainable by radiography except when the abscess has become partially encysted, when the outlines become apparent to X-rays. Occasionally, however, as in a recent case of the Editor's, the outline of the liver abscess may show up as a more opaque area in the liver substance giving the exact location to the exploring syringe. Occasionally, too, after aspiration there is secretion of gas into the abscess cavity which presents a translucent appearance to X-rays. A blurring of the outline of the diaphragm occurs if the abscess is situated near the upper surface of the liver. The cardiophrenic angle becomes less acute and more approaching a right angle, and this may form a valuable indication in the X-ray appearances. In abscesses of long standing the margins of the cavity may become cretified and may then become visible to the rays, or it may present itself as a definite opacity (Plate XVIII).

The bromsulphalein and other liver function tests, as an indication of hepatic disease and liver abscess, have so far proved disappointing.

Perhaps the most common error is to regard the hectic fever of liver abscess as attributable to *malaria*. The regularity with which the daily fevers recur, the daily chilliness or even rigor coming on about the same hour, the profuse sweating, and other circumstances so compatible with a diagnosis of malaria, all contribute to this mistake. So common is the error that Osler said he hardly ever met with a case of liver abscess which had not been drenched with quinine; and this has been the experience of others. Medical men have made this mistake not only in their patients but in their own persons. The periodicity of the fever, and the presence of a polymorphonuclear leucocytosis should obviate so serious an error.

To mistake other forms of suppuration for liver abscess is of no great moment, because in many suppurative diseases the treatment is the same as for liver abscess, and no bad result need be looked for if diagnosis is not quite accurate.

Intrahepatic suppuration may occur in ascaris infection, in melioidosis (p. 307), as the result of ascending pylephlebitis, as a metastatic phenomenon to diverticulitis and, rarely, by suppuration caused by a hæmolytic *Staphylococcus aureus*. Large suppurating abscesses have been reported secondary to duodenal ulceration. Carcinomatoses of the liver unaccompanied by jaundice may simulate amœbic abscess and, occasionally, a suppurating gumma. A right perinephritic abscess may have to be considered, and the Editor has had a case which had been opened from above the diaphragm in the belief that the abscess was primarily hepatic. Subdiaphragmatic abscess may have to be considered also; this is most commonly caused by perforation of a gastric or duodenal ulcer. An abdominal swelling can usually be recognized occupying a triangular area on the affected side. Gas is usually present and can be recognized by a resonance in

the upper part of the swelling, which should distinguish it from liver abscess.

A serious error, however, is to overlook the presence of leucocythæmia, kala-azar, pernicious anæmia, or scurvy, and to proceed to aspirate an enlarged liver on the supposition that the symptoms arise from abscess.

Amœbic abscess of the liver which has ruptured through the diaphragm may have to be differentiated from many other pulmonary conditions, such as broncho-pneumonia, tuberculosis, actinomycosis, and malignant disease of the lung.

Diagnostic aspiration.—In order to make the diagnosis of liver abscess certain, aspiration must be resorted to. When the needle enters the liver, an up-and-down pendulum-like movement will be communicated to its outer extremity, in harmony with the rising and falling of the organ in respiration. If the needle does not exhibit this movement, its point may be in an abscess cavity, but such an abscess is not in the liver.

Prognosis.—The prognosis in early operations on single abscess of the liver, provided there is no dysentery or other complication, is good. In multiple abscess, or in single abscess, if there is active dysentery or other serious complication, the prognosis is bad ; if there are more than two or three abscesses, it is usually hopeless.

The *question of return to the tropics* after recovery from liver abscess frequently crops up. If feasible, and if the patient has not to make too great a sacrifice, he ought to remain in a temperate and healthy climate. There are many instances, however, of individuals who have enjoyed permanent good health in the tropics after recovery from liver abscess. Before giving permission to return it should be ascertained whether the bowel is thoroughly cleansed of amœbic infection. Neglect of this precaution may lead to reinfection from the bowel and recurrence after a period of seven years from the formation of the first abscess.

Treatment.—Hepatitis which has not proceeded to abscess-formation should be treated, especially if dysentery be present or has been antecedent, with full doses of emetine, repeated once or twice a day for two or three days or longer, by a cautious use of the purgative sulphates, and with poultices, rest, and low diet (*see* p. 544). Emetine should be injected in 1-gr. doses up to a total of 12 gr., and if cysts of *E. histolytica* are present in the stools, by a combined course of E.B.I. and yatren (quinoxyl.) If there be much pain, relief may be afforded by either wet- or dry-cupping over the liver, or by leeches. Ammonium chloride, 20-gr. doses, three times a day, is also commonly prescribed.

When the occurrence of rigor, or the development of hectic fever, or the appearance of local bulging, or the persistency of the fever and of the local symptoms, gives ground for suspecting that abscess has formed, active medication must be suspended, and measures taken

without unnecessary delay to locate, by means of the aspirator, the position of the pus.

Preliminary aspiration.—When he uses the aspirator the surgeon must be prepared to continue till all the pus is evacuated, or under exceptional circumstances, operate.

Deep cocaine anæsthesia usually suffices, but nervous subjects should undergo general narcosis. A medium- or full-sized aspirator needle should be used, as the pus, owing to its nature, may not flow through a cannula of small bore.

If there are localizing signs, such as a tender spot, a fixed pain, a localized œdema, localized pneumonic crepitus, pleuritic or peritoneal friction, these should be taken as indicating, with some probability, the seat of the abscess and the most promising spot for exploratory puncture. If none of these localizing signs is present, then, considering the fact that the majority of liver abscesses are situated in the upper and back part of the right lobe, the needle should, in the first instance, be inserted in the anterior axillary line in the 8th or 9th interspace. Effusion of serum into the pleural cavity immediately adjacent to the liver abscess sometimes occurs.

In cases with cardiac or pulmonary embarrassment, aspiration can be efficiently carried out under local infiltration of skin and muscles with 2-per-cent. novocain, to which is added 1 : 1000 adrenalin in the proportion of 10 drops to the ounce. The passage of the needle through the liver substance is painless. Should, however, the abscess point into the abdominal cavity, a general anæsthetic is advisable, for an open operation may become necessary. Occasionally the pus proves to be so viscid that complete evacuation takes an hour or more to complete; in these circumstances eusol in saline (half-strength) should be injected into the abscess cavity in order to dilute it.

A thorough course of combined emetine-bismuth-iodide and quinoxyl should be given as an after-treatment to operation in order to eradicate the infection from the bowel.

Open operations.—The open operations for liver abscess performed in English practice will now be described. The choice of the anæsthetic must be left to the surgeon. If general anæsthesia is desired, gas and oxygen may be used, but success is usually obtained by means of deep infiltrating local novocain anæsthesia.

The route for opening the thoracic or abdominal wall varies according to circumstances as follows:

Transperitoneal route.—When pus is struck below the costal margin, the aspirator needle is left *in situ* and the abdomen is incised for a length of 3 in., the intestines being guarded with packing. If adhesions are present, a sinus forceps is directed along the needle and pushed through into the abscess, and the blades are opened after withdrawal of the needle. The finger should be inserted into the abscess cavity. When the first gush of pus ceases, the exit is lightly plugged with gauze and the margins of the liver wound are carefully sutured to those of the parietal peritoneum, and the remainder of

the wound closed. The gauze plug is now removed, and a wide drainage-tube, provided with a flange and lateral openings, is introduced to the bottom of the abscess cavity.

Transpleural route.—Should the abscess be struck through an intercostal space, a couple of inches of rib had better be resected. The diaphragm should then be stitched to the thoracic wall, or, better, to the skin as well, when the abscess may be opened with a forceps. An attempt should be made to stitch the capsule of the liver to the diaphragm. Should the pleura be opened, pneumothorax will result, but this is not necessarily a serious contingency. On no account should pus be permitted to enter the pleural cavity.[1]

Treatment after operation.—For the first two days after a liver abscess has been opened the discharge is considerable, and the dressing may have to be changed frequently. Very soon, however, should the case do well, the discharge rapidly diminishes, and the dressing requires renewal only every other day, or every three or four days. During the first week the drainage-tube, provided it be acting efficiently, should not be disturbed, more particularly as it may be difficult to replace. Later, it may be removed and cleaned, and, when discharge has practically ceased, cautiously shortened. *It is a great mistake to begin shortening the tube before it is being pushed out, or so long as there is any appreciable discharge.* If there is the slightest indication, such as rise of temperature, that pus is being retained, the drainage must be rectified and the sinus, if necessary, dilated with forceps and finger, and a full-sized drainage-tube introduced as far as it will go. If this does not suffice, a counter-opening may have to be made. *Delay in remedying imperfect drainage is a serious—it may be fatal—error.*

Should an abscess on being opened be found to be septic, or should it become so, it must be flushed out daily, or twice a day, with a weak non-mercurial antiseptic, and a counter-opening made if necessary. Continuous drainage by the Carrel-Dakin tube method and daily eusol irrigation is often very successful. Where there is a thick necrotic zone delimiting the abscess, this continuous irrigation is highly necessary, and in order to dissolve the thick pus the injection of a ferment—enzymol (Fairchild) in the strength of 1 drachm to the ounce of water—is a useful adjunct.

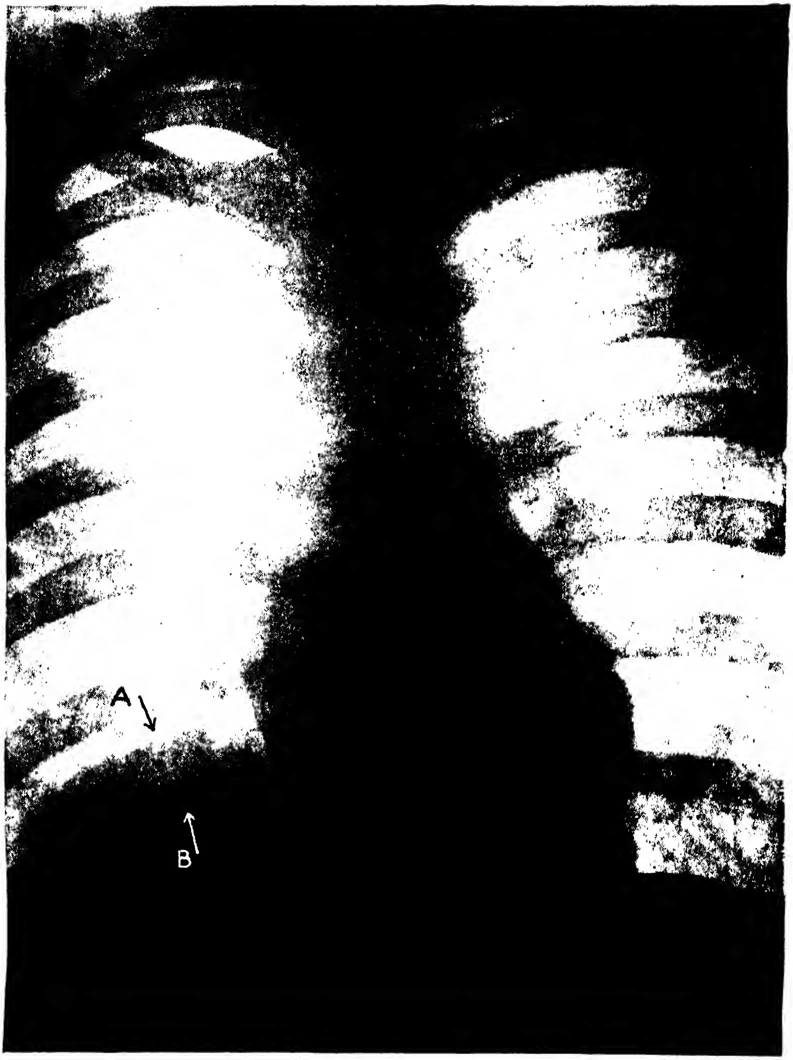
After a liver abscess has been opened and is draining well, temperature rapidly falls, and in a few days, or almost at once, becomes normal. Should fever persist, it is to be inferred either that the drainage is inefficient, or that there are more abscesses in the liver, or that there is some complication. If it be deemed that there is another abscess, this should be sought for with the aspirator and, if found, drained.

It is advisable to give emetine in 1-gr. doses hypodermically, both before and after operation, and continue it for a fortnight, whichever operation is employed.

If any symptoms of hepatic inefficiency due to extensive destruction of liver tissue are noted, the presence of diacetic acid or a high ammonia coefficient in the urine should form an indication for the oral or rectal administration of glucose and sodium bicarbonate, or in some cases for the intravenous injection of these drugs in 5- to 10-per-cent. solution.

Discussion on the merits of various recognized methods of treatment in liver abscess.—The question is frequently and very reasonably

[1] If pleural and peritoneal adhesions are not present, it is usually advisable to pack the cavity with gauze, and complete the operation in two days' time.



Radiograph of liver abscess bursting through the diaphragm into base of right lung, whence the pus is being evacuated through a branch of the right bronchus. A collection of pus in pleural cavity; B—valve-shaped opening through diaphragm at site of abscess in liver. *(Orig. case. Radiograph by Dr. M. Berry.)*

LIVER ABSCESS.

PLATE XIX

asked why so many methods of treatment, medical as well as surgical, are employed in the treatment of liver abscess, and only some abscesses respond apparently to injections of emetine while in others the course of the disease is in no wise modified by this drug. The answer appears to the Editor to be moderately simple. The Editor regards the aspiration of the abscess cavity by Potain's aspirator to be the safest and most easily executed method. Sometimes more than one aspiration has to be carried out. If the pus is very thick, aspiration may be difficult and may be facilitated by injection of dilute eusol into the abscess cavity, so that after aspiration a course of emetine-bismuth-iodide and yatren may cure the patient permanently and there will be no recurrence. In the Editor's experience almost 28 per cent. of cases diagnosed as hepatic abscess resolve with emetine-therapy (12 gr.) followed by the customary combined treatment. In these probably the formation of pus has not been extensive and the amœbæ are still active. In 47 per cent., aspiration with Potain's aspirator, combined with emetine treatment, is successful. There still remains a proportion of cases (25 per cent.) in which open operation has to be resorted to and emetine therapy has no appreciable effect whatever. These are the cases where a large amount of pus is present and where it is usually secondarily infected with streptococci, *Bacillus coli* and, as in a recent case, with *B. enteritidis*. It is disappointing to have to record that previous thorough treatment of intestinal amœbiasis with E.B.I. and yatren does not always prevent the subsequent development of hepatic abscess. The Editor has had this experience on three occasions, while Biggam has reported it twice.

Treatment of abscess discharging through the lung.—In the case of abscess discharging through the lung and, although emetine has been freely administered, not progressing favourably, the question of obtaining more efficient drainage by surgical means must be considered. There are two possibilities which render interference desirable: (*a*) Continued discharge of pus and blood, with or without attendant hectic fever; a condition which, if it persist, will, in all probability, in the end, kill the patient. (*b*) Not infrequently, prolonged discharge through the lung may induce fibrotic changes in that organ, or may give rise to pneumonia, or to abscess of the lung with all its attendant dangers, such as thrombosis or abscess of the brain. (Plate XIX.)

In all cases of abscess discharging through the lung a careful register should be kept of three things—body-temperature, daily amount and character of expectoration, and, once a week, the weight of the patient. If temperature keeps up, if the amount of pus continues the same or increases, or if the patient continues to lose weight, an attempt should be made at all risks to reach and drain the abscess from the outside. If temperature remains normal, if pus gradually or intermittently decreases, and if the body-weight is maintained or increases, operation is unnecessary, or, at all events, should be deferred.

Medicinal treatment with full doses of ipecacuanha and emetine, maintained over a long period, generally exerts an instantaneous and almost miraculous effect upon these cases, and renders operative interference inadvisable.

In exploring the liver in such cases, it must be borne in mind that most likely the abscess cavity is collapsed, and that the sides of the abscess may be in contact. Such an abscess is not likely to be discovered unless the needle be thrust into its full extent and, whilst a good vacuum is being maintained in the aspirator, slowly withdrawn. If by good fortune the abscess has been traversed, then, when the end of the needle is crossing the cavity, a small amount of pus will be seen to flow.

Treatment of abscess rupturing into a serous cavity.—When there is evidence that an abscess of the liver has ruptured into the peritoneum, into the pleura, or into the pericardium, the particular serous cavity involved must be opened at once and treated on general surgical principles; otherwise the patient will almost surely die. In the circumstances the surgeon will be justified in assuming great risks.

2. AMŒBIC ABSCESS OF THE BRAIN

According to Armitage, 48 cases of amœbic abscess of the brain have been recorded, for the most part from Egypt. Like hepatic abscess, it is more common in men than in women. It is generally solitary, and may be regarded as a metastasis of hepatic abscess. During life it gives rise to various cerebral pressure symptoms and is invariably fatal.

3. AMŒBIC INFECTION OF THE SKIN AND SUBCUTANEOUS TISSUES

Since 1892, it has been known that occasionally amœbic invasion of the skin in the vicinity of a discharging liver-abscess sinus may take place. When recognized, the amœbæ may be demonstrated in sections of the skin, and they are extraordinarily susceptible to the action of emetine. Gangrenous lesions of the abdominal wall and perineum have been noted from time to time, especially by Engman and Meleney (1931). Hsu in Peiping, China, has described a series of fourteen cases and has shown that the condition is by no means rare.

Amœbiasis cutis occurs as a secondary infection of papillomata in the anal region. The lesions are punched-out, resembling in this respect amœbic intestinal ulcers. The author had a case, involving the parietes in the vicinity of a colostomy and invading the abdominal wall (Fig. 66), in a patient who was proved to have active amœbic dysentery. The response to emetine therapy was instantaneous, and almost miraculous. A very extensive gangrenous destruction of the buttocks and skin of the back was seen in St. Mark's Hospital, London, in an ex-soldier who had served in India fifteen years previously. He had never suffered from amœbic dysentery, though *E. histolytica* cysts were present in the fæces. The lower part of the rectum, the pelvic floor and the perineal tissues had been destroyed. In this case, also, the response to emetine therapy was remarkable.

4, 5. AMŒBIC ABSCESS OF THE SPLEEN AND OF THE EPIDIDYMIS

Of these complications, the former, which is very rare, is usually associated with hepatic abscess. The latter has once been reported in a case from China by Warthin.

6. URINARY AMŒBIASIS

A number of uncritical papers have appeared from time to time describing as amœbæ in the urine large prostatic or other inflammatory cells which may be present in subacute cystitis or prostatitis. When genuine E. *histolytica* in the vegetative form is present in the urine,

Fig. 66.—Amœbic granuloma and ulceration of abdominal parietes surrounding colostomy.

it is due to a fistula between the bladder and the ulcerated rectum, as in the case reported by Craig (1911). Amœbic ulceration of the urethra in the male, as well as of the cervix uteri in the female, has been reported by Hsu in China, and the amœbæ have been demonstrated in microscopic sections. There is no evidence at present that embolism of the kidney vessels by amœbæ derived from bowel ulceration does take place, as suggested by Manohar (1936).

7. PULMONARY AMŒBIASIS

The type of case designated under this heading is quite distinct from those of pulmonary abscess secondary to the liver, in which infection of the lung tissue results as direct extension from the hepatic abscess or by actual rupture into the bronchus.

In primary pulmonary amœbiasis it is assumed that the entamœbæ reach the lung by direct embolism from the gut-wall. Having gained the pulmonary circulation, they form firm consolidated nodules, which later break down into small abscesses. The symptoms produced in these cases, of which the Editor has reported three, resemble closely those of a fugitive broncho-pneumonia or some form of tuberculous infiltration.

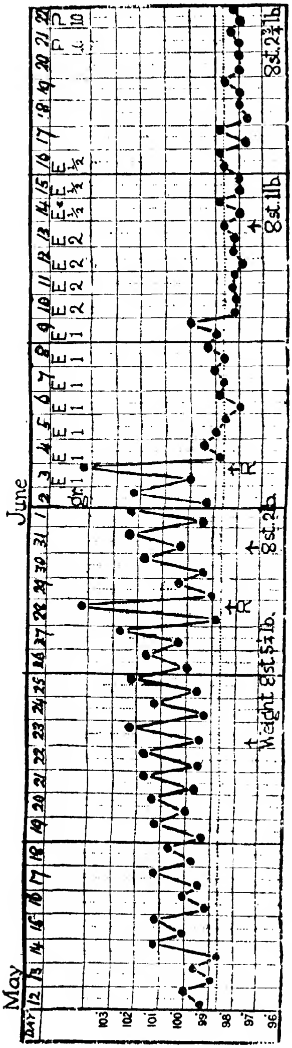


Chart 24.—Pulmonary amœbiasis with broncho-pneumonic symptoms and signs. Immediate improvement after institution of emetine treatment. (*Orig. case, from "The Lancet."*)

The patients, who have been at some time the subjects of amœbic infection, commence to suffer from pulmonary symptoms, with profuse purulent expectoration, sometimes tinged with blood, and, it may be, respiratory distress and intermittent pyrexia. They are, however, subject from time to time to violent rigors, a feature which serves to differentiate these cases on clinical grounds from other respiratory diseases which they may closely simulate. The physical signs produced in the lungs vary very much, but are usually those of broncho-pneumonic consolidation, patches of which are usually detectable at the border of the scapula, especially on the right side. Skiagraphy is of little avail in diagnosis. The entamœbæ have, so far, not been found in the sputum, though there is, as a rule, a distinct leucocytosis. The response to emetine or ipecacuanha treatment is as rapid as it is remarkable (Chart 24). A full course of emetine injections should be given.

BALANTIDIAL DYSENTERY

The occasional occurrence of *Balantidium coli* in the fæces, particularly in association with dysenteric diarrhœa, has been recognized for the last fifty years. It is only since Strong and Musgrave called attention to the subject that *Balantidium coli* has come to be regarded as the germ cause of a particular type of colitis resembling in many

respects amœbic dysentery. The parasite has been studied from the zoological standpoint, more especially in temperate climates, but it seems probable that extended observations will show that the balantidium is equally if not more prevalent in warm climates. It is a common parasite of the pig, and produces a fatal form of dysentery in monkeys in captivity, especially chimpanzees. Human cases have been reported all over the world, but especially from Germany and France; those who tend domestic pigs are exceptionally liable. Mackenzie and Bean (1938) recorded the first case in England in a mental patient.

How it attains the human intestine is not known, but as it is a common parasite of the pig, these animals are the usual source of infection, although the balantidium may live for a considerable time in water or fæces (one hour to three days). In liquid stools it exhibits great activity, indulging in locomotive as well as in rotary movements.

The parasite has been grown on artificial media by Barret and Yarbrough, using a mixture of inactivated human serum with 0·5-per-cent. of salt solution in the proportion of 1 : 16.

For description, *see* p. 870.

Geographical distribution.—According to Prowazek, balantidiasis in man has been recorded from Russia, Scandinavia, Finland, Germany, Austria, Holland, Italy, Siberia, China (Tsingtau), Georgia, the Philippines, Cochin China, Andaman Islands, Sandwich Islands, Egypt, and the Sudan. Two cases have been reported from North America, others in Brazil, Porto Rico, and Cuba, and one from England.

Pathology.—In the gross as well as in the microscopic pathology there is little or nothing to distinguish the structure from that of amœbic ulceration; the organisms have been found by Martini and Walker in the substance of the mesenteric glands.

In thirty cases in which autopsies have been made, a variety of dysenteric lesions, from catarrhal congestion and diphtheritic patches to extensive ulceration, were found. On section, Strong demonstrated the balantidium, not only in exudates on the surface of the bowel, but congregated in large numbers in the follicles, and embedded in the tissues forming the base of the ulcerations, including the submucosa and muscular coat, and even in the lumen of blood-vessels and lymphatics. Bowman stated that the colon may be affected throughout its whole extent with a mass of ulcers from which hang shreds of necrotic tissue—lesions resembling those of amœbic dysentery.

Symptoms produced by balantidial dysentery are, in the present state of knowledge, indistinguishable from those of amœbic dysentery. The disease is chronic in type, its special nature being discoverable only on microscopic examination of the stools. Generally only one or two balantidia are found, but as many as twenty may be seen in every field of the microscope. The blood usually shows no change; there is no leucocytosis and the polymorphs number 70 per cent. The appearance of the ulcerations in the bowel, as seen by sigmoidoscopy, resemble those of intestinal amœbiasis as described by Mazza, Alvarado and Schürmann (1932).

Treatment.—Walker finds from his experimental work that organic compounds of silver are the most effective in eradicating the infection. Thymol has been recommended, and oil-of-chenopodium treatment, as in ancylostomiasis, has been reported to be successful. Emetine injections are said by Kipschidse in Georgia to give the best results. Carbon tetrachloride,

in drachm doses, followed by salts, is claimed to be effective in Egypt. Yered has tried a new remedy—Carobinase—a watery extract of *Jacaranda decurrens*, 25 grm. in 500 c.c. of hot water, which is given as rectal lavage for three weeks.

III. HELMINTHIC DYSENTERY

Bilharzial dysentery.—Adeno-papillomata or ulcerations of the large intestine caused by the passage of eggs through the coats of the intestinal wall, occur in infections with *Bilharzia mansoni*, *B. japonica*, and exceptionally with *B. hæmatobia*. The form of dysentery produced by these lesions is met with in those countries in which these parasites occur.

The stools typically contain yellow or bile-stained mucus with clots or streaks of blood, in which the eggs can be found under a low power of the microscope. Eosinophilia in the blood, together with symptoms of dysentery, is highly suggestive, and the diagnosis should, if possible, be confirmed by the discovery of the characteristic eggs in the fæces. A sigmoidoscopic examination by which the characteristic lesions may be visualized will help in doubtful cases. In making a microscopic examination of the fæces, the pathologist should remember that the eggs are more easily found in the outer zone of solid fæces than in more fluid portions (*see* p. 735). Usually the pus cells in the fæces contain a high proportion of eosinophiles.

Infection with Œsophagostomum apiostomum and O. stephanostomum (p. 937).—These are rare intestinal parasites of man in Northern Nigeria and Central Africa, but when present in large numbers they give rise to dysenteric symptoms. The adult worms encyst under the submucosa, and may, together with its eggs, be recognized in the dysenteric discharges.

Infection with other helminthic parasites.—Chronic diarrhœa and dysenteriform attacks are occasionally noted in intestinal infections with *Fasciolopsis buskii* (p. 894), *Paragonimus westermanii* (p. 901), *Heterophyes heterophyes* (p. 899), and *Strongyloides stercoralis* (p. 839).

DIFFERENTIAL DIAGNOSIS OF THE DYSENTERIES

Mixed infections of all the different forms of dysentery may, of course, occur in those countries in which these diseases are endemic.

Double infections of amœbic and bacillary dysentery are the most frequent. Such cases do not usually occur in temperate countries, but during the course of severe epidemics of bacillary dysentery, when bacillary infection may supervene upon a long-standing amœbic ulceration of the bowel. On the other hand, a bacillary infection may be followed by an amœbic invasion of the bowel, which makes the matter of diagnosis more difficult still.

Bacillary dysentery occurs commonly as a terminal event in intestinal bilharziasis, and amœbic ulcers are sometimes recognized as a concurrent infection in the same condition.

"**Giardiasis.**"[1]—In addition to *E. histolytica, E. coli,* and *Balantidium coli,* certain other protozoa occur from time to time in the intestinal canal and appear in the fæces. Of these, perhaps *Giardia* (*Lamblia*) *intestinalis* has the best claim to be regarded as pathogenic. The usual habitat of the parasite is in the upper part of the small intestine, but it may also heavily infest the duodenum. When newly passed in the fæces it is very active, presenting a characteristic appearance. During the passive stages the cysts appear in the fæces in enormous numbers, and are often associated with those of *E. histolytica.* They are generally found in the fæces of about 4–16 per cent. of normal natives of the tropics. Other forms are found in mammals and in reptiles, and one in the mouse, *Giardia muris,* is closely allied to the human form. In children giardia infection is three times as common as in adults. (In America 48·1 per cent. of industrial school children.) For a description of the parasite, *see* p. 866.

Numerous observers have brought forward evidence of the pathogenicity of the parasite on the grounds that it is found in an active state and in large numbers when the stools are liquid, and that quantities of mucus are passed containing numerous parasites.

In England and in Canada the parasite has been found in the intestine of a large percentage of normal children, while Boyd, Silverman, and others have shown that it can be demonstrated quite commonly in the duodenal juice removed by Einhorn's tube, as well as in the bile; it has also been recorded in the gastric contents.

Giardia infection is associated at times with a type of recurring diarrhœa accompanied with abdominal discomfort. The stools may be of a peculiar clay colour and of a pultaceous consistence, and may resemble those of sprue or, in children in England, cœliac disease (R. Miller, 1926). On recovery from one of these attacks only the encysted forms can be found. Relapses of a periodic type tend to occur, but eventually tolerance of the parasite appears to be acquired. Flatulency is almost invariably present and escapes when the stool is passed. In the acute stage the abdomen is tender and there is general discomfort. The attack is not accompanied by emaciation, and symptoms probably originate from the mechanical action of the parasite, and not to an actual lesion of the mucosa, though in mice, in which these parasites cause diarrhœa, they may be found in the submucosa in sections of the gut. Giardia infections are especially intractable and may persist for years. Hegner considers that the number of these parasites is dependent upon the diet of the individual, for they disappear from the fæces when the patient is fed upon a meat dietary.

Treatment.—It is extremely difficult to be certain that complete extirpation of these protozoa has been procured, for giardia frequently reappear in numbers in the fæces after an absence of several months. Apparently the parasite itself is subject to periods of great activity followed by periods of quiescence.

A form of treatment which so far has appeared to be successful in the Editor's experience is high colonic lavage by means of the apparatus known as the Studabath. Large quantities of fluid, 10–20 litres, are run continuously into the large bowel by means of a two-way pipe, an hour or more being

[1] Giardiasis or lambliasis is mentioned in this section for the sake of completeness, although the diarrhœa associated with the parasite cannot strictly be classified as a dysentery.

taken over the process. The fluid employed is a solution of chamomile (*Kamillosan*). Several of these treatments have to be given. Local treatment should be combined with a high protein dietary, consisting mostly of red meat (Hegner).

Bismuth salicylate may also be given in drachm doses three times daily.

L. Brumpt advocates quinacrine (the French preparation of atebrin) by the mouth in tablet form, in therapeutic doses, as specific for this parasite. Recently other observers have substantiated this claim, and it appears that in atebrin we have the long-sought-for specific drug for giardiasis. It appears to be effective when given by the mouth or injected subcutaneously in the form of the *musonate*. The course is described by Garin and Mafli as follows: Three 10 cgm. tablets of quinacrine (atebrin) for five consecutive days; for children of ten years or more, 2 tablets, one at midday and one in the evening for four days.

OTHER FORMS OF DIARRHŒA AND DYSENTERY ASSOCIATED WITH INTESTINAL PARASITES

The common intestinal flagellates, *Trichonomonas intestinalis* and *Chilomastix mesnili* (*see* pp. 864–5), though occurring commonly in diarrhœic and dysenteric stools, have little claim to pathogenicity; they are frequently present in large numbers in the fluid fæces of patients convalescing from bacillary or amœbic dysentery. Probably the presence of large numbers of these flagellates in the bowel contents is due, to a great extent, to the fluid medium in which they live; but when a case of chronic diarrhœa is encountered in which no other obvious signs can be found, and where large numbers of active flagellates are lashing about in the liquid fæces, it becomes difficult not to assign a pathogenic rôle to these apparent agents of disease. Hence the term **flagellate dysentery,** a term which probably designates that the human host has been exposed to an abnormal degree of intestinal infection. As regards treatment, these organisms disappear after vigorous lavage of the intestinal canal by irrigations of 2-per-cent. sodium bicarbonate, aided by stovarsol (gr. 4), or spirocid, in similar dose—two tablets daily, given by the mouth, for eight to ten days.

Spirochætal dysentery is said to be due to the presence of numbers of spirochætes in the intestinal canal. These organisms are composed of three or more simple spirals, and are known as *Spirochæta eurygyrata*, but they are not now regarded as pathogenic.

Intestinal coccidiosis has to be considered, especially the organism known as *Isospora* (*see* p. 868), which causes diarrhœa with mucus and appearance of Charcot-Leyden crystals in the excreta. Cases have been reported from all over the world, but especially from the Near East and the Dutch East Indies.

"**Malarial dysentery.**"—A blood-stained discharge, or more frequently intestinal hæmorrhage, may occur in the abdominal forms of subtertian malaria; the blood passed is very dark, due to petechial hæmorrhages into the intestinal mucosa. These are, as a rule, very serious cases. Instances have been recorded by the Editor in which malaria was first suspected by the discovery of the parasite within the red blood-corpuscles passed per rectum. Besides the hæmorrhagic appearance of the fæces, the clinical

aspect of the patient, the sweating, the icteric tint of the sclerotics and skin, and the enlarged spleen should suggest malaria. *Violent diarrhœa* may be the one outstanding clinical sign of an intensive subtertian malaria infection.

"**Kala-azar dysentery.**"—Blood and mucus may be passed in the fæces in advanced cases of this disease; this is thought to be due to an ulceration of the bowel by the Leishman-Donovan body. The parasites are present in large numbers in the villi of the small intestines, and may even form polypoid masses in the mucous membrane of the large intestine, and have been found in the fæces.

Other conditions which may resemble dysentery.—There are other perhaps more familiar conditions, not necessarily of tropical origin, in which dysenteric symptoms may occur. They must be briefly mentioned.

Of all familiar diseases with which dysentery of a mild form is confused, the first place must be given to *internal hæmorrhoids.* In this instance a correct diagnosis is readily made. Again, profuse offensive diarrhœic motions with blood and mucus may be passed in *tubercular ulceration* of the large bowel, which is comparatively common in the tropics. *Colitis*, of the ulcerative, membranous, and *hæmorrhagic* varieties, resembles bacillary and amœbic dysenteries in clinical features and in the character of the stools, but can easily be differentiated by microscopic examination of the fæces, as well as by the sigmoidoscope. Idiopathic ulcerative colitis (colitis gravis) is becoming increasingly common. It is undoubtedly a disease *sui generis* and is distinguished by pyrexia, toxæmia, intense anæmia, a tendency to spontaneous cure, and great liability to relapse. A very intense form sometimes arises in uræmic states consequent upon cystoscopy or instrumental investigation of the genito-urinary tract. *Mucous colitis*, or the syndrome which is commonly known under that name, is a frequent *sequel* of both bacillary and amœbic dysentery and is frequently being confused with both. Stercoral ulceration produced by chronic constipation, and often associated with myxœdema, may give rise to a blood-and-mucus discharge. Certain surgical conditions—*simple polypus*, malignant diseases, intussusception or even syphilitic disease of the rectum, or rectal stricture in lymphogranuloma inguinale (p. 660), the diagnosis of which is easily determined by a digital examination—should be kept in mind. *Polyposis* of the intestine is a very distressing condition which may become malignant. A foreign body in the rectum is another possible diagnosis.

Blood and mucus is often passed in the condition known as *diverticulitis*, and this is common in tropical practice. In chronic mercurial poisoning, an ulceration of the large intestine may produce dysenteriform stools, and in paratyphoid infections a similar condition may be met with. Food poisoning due to members of the Salmonella group may sometimes give rise to confusion.

CHAPTER XXIX

SPRUE AND HILL DIARRHŒA

Synonyms.—Tropical Diarrhœa; Aphthæ Tropicæ; Psilosis; Ceylon Sore Mouth.

Definition.—A peculiar and dangerous form of chronic inflammation of the whole or part of the mucous membrane of the alimentary canal. Although a disease of warm climates, it may develop for the first time in temperate countries; only, however, in individuals who have previously resided in the tropics or subtropics.

History.—Sprue was first described by a Dutchman, V. Ketelaer, in 1669, and then by Hillary in Barbados in 1766, but the term "sprue" was first applied to the disease when it was rediscovered independently by Van der Burg in Java, and by Patrick Manson in Amoy, China, in 1880. Since that time, it has been found to be a comparatively common in the tropics. A somewhat similar disease has been recognized in northern Europe and has been termed "non-tropical sprue" by Thaysen in 1932.

Geographical distribution.—South China, Manila, Cochin China, Java, the Straits Settlements, Ceylon, India, Mauritius, a few cases from Fiji, the West Indies, the Southern United States, Porto Rico, Central America, the Guianas, and Queensland. Recently what appear to be authentic cases have been recorded from Iraq, Egypt and Malta. The Editor has seen one mild case from Nyasaland, but authentic records of sprue in North and Central Africa, Palestine, and Arabia are rare.

Epidemiology and endemiology.—Information so far amassed on this subject points to sprue being a regional, as opposed to a climatic disease, and it is one which pre-eminently affects Europeans. Doubt was formerly expressed as to the existence of sprue in native races, but the fact is that dark-skinned people, usually indigenous inhabitants of the endemic country, are less liable to be attacked than are immigrant races.

The disease is often apt to occur in one or more members of the same family. Many instances of sprue developing in husband and wife have been recorded; it is probable that both have been exposed to the same influences. Atmospheric temperature does not influence the incidence of the disease, for sprue originates at high altitudes in Ceylon and in the Himalayas where the climate more resembles that of Europe.

There are residences in Bombay and bungalows in Ceylon which are notorious for the incidence of sprue in successive tenants, and the term "sprue houses" has been applied to them. In Ceylon there is a widespread belief that it is connected with dry-rot in estate "bungalows," and F. P. Jepson has brought forward circumstantial evidence that the white ant or termite, which bores its way into the wood, is in some way connected with sprue. Certainly the successive occupants of such houses appear to be specially liable. The "dry-rot" at elevations of 3,000 feet is caused by termites belonging to the genera *Cryptotermes* and *Planocryptotermes* and it is suggested that the ingestion of the fæcal pellets of these dry-wood-inhabiting ants might be responsible for the causation of sprue. In the main, foci of distribution of sprue are the regions in which dry-wood termites are common.

As a rule, sprue attacks those of middle age, but it has been recorded in a European boy of eleven (Miller). Amongst Europeans, at any rate, the female sex appears to be more liable to the development of the disease.

Ætiology. The ætiology of sprue is still obscure. It is generally agreed that it is a disease *sui generis*. The yeast, or *monilia* theory of sprue has been abandoned. This yeast, originally found by Kohlbrügge in 1901, and later named *Monilia psilosis* by Ashford, was found by the Editor to be a terminal infection. A *vitamin-deficiency* has been suggested by MacCarrison, founded upon experimental work in monkeys.

Scott's hypothesis.—H. H. Scott, impressed by the similarity between many of the symptoms of sprue and those occurring in other diseases in which calcium deficiency and a disordered calcium regulation play a part, suggested that the essential factor was a calcium deficiency. Such symptoms as tetany, cramps, loss of weight, and œdema, which may be present in sprue, lend a certain amount of support to his fundamental idea.

As the result of combined clinical and pathological observations, sprue is regarded as definitely due to some infective agency which especially involves the mucosa of the alimentary canal, and this view receives some support from the fact that hill diarrhœa is a frequent precursor of sprue, and it is considered that the phenomena of sprue can best be explained in terms of a metabolic breakdown of the gastro-intestinal tract, characterized by defective absorption in the small intestine.

In the Editor's experience there is a considerable amount of evidence of the close association between sprue and amœbic dysentery and other intestinal diseases. The two diseases often co-exist, while on occasions sprue appears to be grafted on intestinal amœbiasis, but this may be purely coincidental. Possibly, too, in the apparent absence of sprue from Central Africa may lie the clue to its true ætiology.

The *vitamin deficiency* hypothesis rests upon the similarity, in some respects, between sprue, pellagra, and idiopathic steatorrhœa, which are considered to be examples of combined deficiencies; and, also, because secondary vitamin deficiencies are frequently encountered in the fully developed disease.

Pathology.—Post mortem, the tissues in sprue are abnormally dry; fat is almost completely absent; the muscles and the thoracic and abdominal viscera are anæmic and wasted. The liver is atrophied to half its normal weight, or even less; the spleen, adrenals, heart, and in fact all the viscera, are wasted approximately to the same degree. The heart has, as a rule,

undergone "brown atrophy." With these exceptions and certain changes in the alimentary tract, so far as is known, there are no special lesions which are invariably associated with this disease. Occasionally certain changes are present in the pancreas—namely, fatty or granular degeneration of the cells, with softening of isolated acini and slight inflammatory infiltration of the connective tissue. These, however, are not more constant than are similar changes occasionally found in the liver and kidneys. Sections of

Fig. 67.—Transverse section of ileum in case of sprue, showing partial loss of columnar epithelium (probably a post-mortem change), shrinkage of villi, round-cell infiltration, fibrosis of submucosa, and dilatation of nutrient vessels of submucosa. (*Orig.*)

the tongue show desquamation of the epithelium, especially from the surface of the fungiform papillæ, which may be infiltrated with yeast fungi.

Lesions of the alimentary tract.—In longstanding cases, there is usually atrophy of the small bowel so as to render it almost diaphanous. Ulceration and erosion of the ileum leading to perforation and peritonitis have been described by the Editor, but these, as well as the destruction of the intestinal villi, are now thought to be secondary changes (Mackie and N. H. Fairley, and, more recently, Thaysen). The chief lesions are thinning and atrophy of the mucous membrane of the absorptive and secretory epithelium (Fig. 67).

The changes are essentially those of degeneration and aplasia and they find evidences of blood destruction in the mucosa, suggesting the absorption of some hæmolytic substance in the intestines and destruction of blood *in situ*. In recent autopsies, where death has been sudden, it is surprising indeed what few naked-eye changes can be seen. Pathological changes are seen in the red marrow of the femur and the tibia. This is usually reduced in quantity, though there may be hyperplasia, as seen in pernicious anæmia. It is suggested that in sprue there is a toxin which primarily stimulates, but eventually exhausts the hæmopoïetic system. Ulceration of the ileum leading to perforation, and general peritonitis may be the cause of death.

The mesenteric glands may be enlarged, pigmented and fibrotic. The inflammatory changes in the mucosa, and the invasion by round and plasma cells which were formerly considered characteristic are now held to be inconstant in appearance and extent, and possibly to be caused by the irritability brought about by the acid content of the fæces. The stools of sprue are characterized by their light colour and excessive size ; they may be five or six times the normal amount.

Analysis of the stools in sprue reveals the presence of the ordinary elements of bile, notwithstanding their apparent absence as indicated by lack of colour. Bile is secreted, but the colouring matter, bilirubin, appears to be reduced in the intestine to a colourless substance, urobilinogen. The excess of fat in the stools and low fat content of the blood (412·8 mg. per cent.) would indicate that a proportion is due to actual excretion of fat through the intestinal mucosa. (The normal is 600 mg. per cent.)

Normally, neutral fats are to fatty acids in the proportion of 1 : 2 : in pancreatic disease this ratio is reversed, and may be as high as 15 : 1 ; while in sprue stools more splitting-up of fats takes place, the proportion of neutral fats to fatty acids being as 1 : 3 or even 1 : 5 (J. D. Thomson). Sokhey and Malandkar, employing Saxon's " wet method " of fæces analysis, find that in a patient on a milk dietary, split fat forms 75 per cent. of the total fat in the stool. The trypsin and other enzyme activities in the stools are normal. These figures indicate that in sprue the pancreatic digestion proceeds quite normally, but that the products of this digestion are not absorbed, probably through the bowel contents being hurried through the small intestine. Malabsorption of fats is probably due to the same cause. Verzár claims that the absorption of fat depends upon the internal secretion of the adrenal cortex ; on the other hand, Barber and Rhoads have demonstrated that the injection of massive doses of liver extract materially affects it.

Symptoms. *Variability*.—There is infinite variety in the combination and in the severity of the various symptoms of sprue, as well as in the rate of progress of the disease. In some instances it may be almost a subacute process, running its course in a year or two ; in others, again, it may drag on intermittently for ten or fifteen years. Much depends in this respect on the circumstances, the character, the care, the treatment, the age and the intelligence of the patient.

General symptoms in a typical case.—In an ordinary fully developed case the patient—who is generally dark or muddy in complexion and much emaciated—complains of three principal symptoms: soreness of the mouth, dyspeptic distension of the abdomen, and looseness of the bowels; the last being particularly urgent during the early morning and part of the forenoon. The patient may also complain of feeling physically weak, of loss of memory, and of inability to take exercise or to apply his mind. His friends will probably volunteer the information that he is irritable and unreasonable.

Mouth lesions.—If the mouth is examined, the soreness will be found to depend on a variety of lesions of the mucous membrane, which, though painful, seem to be of a very superficial character. These lesions vary considerably in intensity from day to day. During an exacerbation the tongue looks red and angry; superficial erosions, patches of congestion, and perhaps minute vesicles appear on its surface, particularly about the edges and tip. Sometimes, from the folding consequent on swelling of the mucous membrane, the sides of the organ have the appearance of being fissured. The filiform papillæ cannot be made out, although here and there the fungiform papillæ stand out, pink and swollen (Plate XX). If the patient be made to turn up the tip of the tongue, very likely red patches of superficial erosion, sometimes covered with an aphthous-looking pellicle, may be seen on either side of the frænum. These aphthæ probably form beneath the epithelium and burst outwards. On eversion of the lips, similar patches and erosions are visible; and if the cheek be separated from the teeth, the same may be seen on the buccal mucous membrane. Occasionally the palate is similarly affected; very often, also, in this situation the mucous follicles are enlarged, shotty, and prominent. The gullet and uvula may also be congested and, in places, raw and sore.

In consequence of the irritation caused by these superficial and exceedingly sensitive lesions, the mouth tends to fill with a watery saliva which may dribble from the corners. If the patient attempts to take any acrid food, strong wine, or anything except the very blandest diet, the pain and burning in the mouth are intolerable; so much so that, although perhaps ravenously hungry, he shirks eating. Not infrequently, swallowing is accompanied and followed by a feeling of soreness and burning under the sternum, suggesting that the gullet, like the tongue, is also in an irritated, raw, and tender condition. During exacerbations of the disease the condition of the mouth becomes greatly aggravated. Although during the temporary and occasional improvements it is much less painful, even then salt, spices, strong wines, and all kinds of sapid foods sting unpleasantly; and the tongue, particularly along its centre, is seen to be bare and polished as if brushed over with a coating of varnish. At all times the tongue is abnormally clean and devoid of fur; during the exacerbations it is red and swollen; but during the remissions, and when

not inflamed, it is small and pointed, and, owing to the anæmic condition of the patient, it may be yellowish like a piece of cartilage. Apparently the tongue condition may at first be the sole outstanding symptom, and may persist for years before the characteristic diarrhœa supervenes.

Dyspepsia.—Dyspepsia is usually much complained of, the feelings of weight, oppression, and gaseous distension after eating being sometimes excessive. Very likely the abdomen swells out like a drum, and unpleasant borborygmi roll through the bowel (Fig. 68). Occasionally though not often, there may be vomiting, sometimes coming on suddenly, and not always accompanied by feelings of nausea. As a rule there is a moderate degree of hypochlorhydria with adequate

Fig. 68.—Sprue abdomen, showing intense meteorism, especially of lower quadrant. (*Orig.*)

response to histamine in the average case of sprue. Occasionally, in early cases, a normal gastric acidity curve is found, but in advanced and especially in very anæmic cases, there is an absolute achlorhydria without response to histamine, resembling that found in pernicious anæmia. The gastroscopic appearances have been described as being similar to those seen in pernicious anæmia, and as taking the form of an atrophic gastritis. The appearances improve under liver therapy.

Anæmia may be pronounced, sometimes even in the early stages of the disease, but more generally it develops when the diarrhœa has persisted for some time. It may be very profound and may approach the pernicious type, with alteration in the size and shape of the erythrocytes and very occasionally by the appearance of normoblasts. It is apparently secondary to an intestinal toxæmia, but sometimes a true *Addisonian anæmia* supervenes after all active symptoms of sprue have disappeared, and such cases are invariably fatal.

The blood picture of the fully-developed sprue case is that of an aplastic megalocytic anæmia. The very variable degrees of anæmia coincide with the variable appearances of the bone-marrow. As a general rule, this graver anæmia occurs in patients over fifty years of age. In no instance in the cases investigated was the colour index less than 0·7. In the majority of cases it is above one. In uncomplicated sprue the leucocyte counts are either normal or there is a leucopenia associated with a relative lymphocytosis. Blood crises commonly occur in sprue and are characterized by a rapid and critical fall in the hæmoglobin and red blood-corpuscles. Usually associated with severe diarrhœa, it progresses to a fatal issue without remissions and without those evidences of blood regeneration which are so typical of similar crises in pernicious anæmia. Hyperbilirubinæmia is found more frequently in malaria and in pernicious anæmia than in sprue. (Van den Bergh test).

The Price-Jones curve resembles that of true pernicious anæmia, being characterized by marked asymmetry, broadening of the base, displacement to the right, and a definite increase of the diameter of the corpuscles to 8·07 μ. It therefore seems that deficient blood-production rather than excessive blood-loss constitutes the basis of sprue anæmia.

The *serum-calcium and phosphorus content.*—Fairley, Mackie, and others have confirmed Scott's observations that the ionic calcium is lowered in sprue, 7·4–9 mg. per 100 c.c. of serum being constantly registered. Fairley and Bromfield, using Kramer and Tisdall's technique, found the average total of calcium was 8·8 mg. per cent. The average serum-phosphorus reading was 3·2 mg. per 100 c.c., so that no rise above normal occurs. It is concluded that defective absorption is the basic factor involved in the low calcium content.

The blood cholesterol.—There is a definite hypocholesterolæmia, and Fairley has shown that the serum cholesterol averages 72·8 mg. per 100 c.c. and the lowest reading is about 40 mg. The cholesterol content rises rapidly following liver-extract therapy and high-protein dietary.

Blood-sugar regulation.—Thaysen originally pointed out that in sprue, as well as in idiopathic steatorrhœa and cœliac disease, there is an abnormally low blood-sugar curve, which is not due to impairment of the glucose absorption or to its destruction in the intestines, but possibly is related to adrenal insufficiency.

The urine is highly coloured, especially in cases with pronounced anæmia. This is due to the appearance of urobilin and urobilinogen in pathological amounts, derived from the products of blood destruction. It is estimated that in sprue anæmia the blood-cells are being destroyed nearly five times as rapidly as in a normal man. The diastatic reaction has been investigated and has been found to be well within the normal limits, and this method affords a means by which sprue may be differentiated from chronic pancreatitis.

The gastric secretion.—In most cases there is a relative hypochlorhydria or a normal acid curve. In cases with severe anæmia there is usually *achylia gastrica.*

Telany associated with dilatation of the stomach is quite common in longstanding cases, and is also found in the early stages where there

has been dehydration of the tissues and hypocalcæmia. It can often be elicited in the hands as Trousseau's sign (i.e. compression of the upper arm).

Cramps in hands and legs may be a particularly distressing feature in an advanced case of the disease.

Diarrhœa.—The diarrhœa associated with sprue is of two kinds—one chronic and habitual; the other more acute and, in the early stages, evanescent. The former is characterized by one or more daily discharges of a copious, pale, greyish, pasty, fermenting, acid, mawkish, evil-smelling material; the latter is of a watery character,

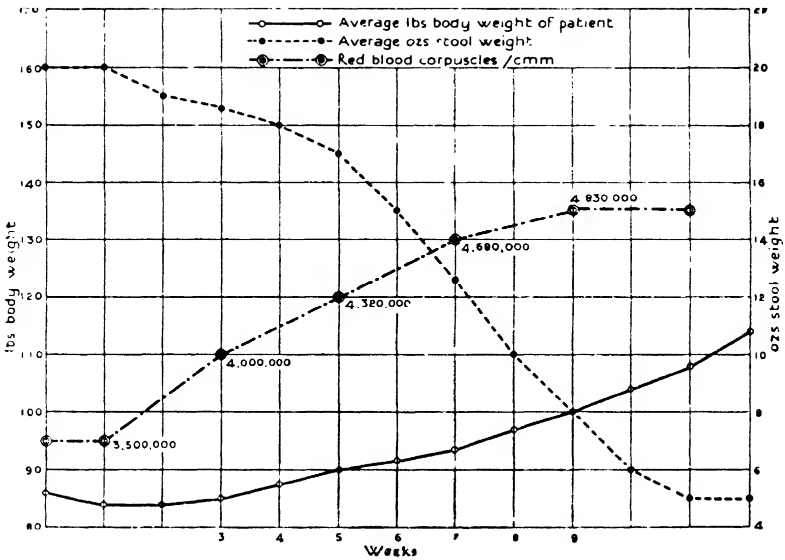


Chart 25.—Composite graph constructed from observations on ten cases, to show the relative increase in body-weight of patient and in red blood-corpuscles per cubic millimetre with coincident decrease in average weight of stool over the same period of treatment. (*Orig.*)

also pale and fermenting, the dejecta containing undigested food and, as a rule, an abnormally large amount of oil and fatty acids. In these latter circumstances the diarrhœa usually brings with it considerable relief to the dyspeptic distension, at all events for a time. When the mouth is inflamed the diarrhœa is usually more active, but this is by no means invariably the case. The stools during periods of quiescence may be confined to one or two in the early morning or forenoon; during the later part of the day the patient is not disturbed. Even in this quiescent phase, however, they are always extraordinarily copious, the excessive bulk being attributable in great measure to the aforementioned excess of fat and to the innumerable microscopic

gas-bubbles; patients remark their phenomenal abundance. They are passed almost, or altogether, without pain. Not infrequently during exacerbations there may be a tender, excoriated condition of the anus, and sometimes, in women, a similar condition of the vagina, causing great pruritus.

Types, history, course, and termination. *Protopathic sprue.*—There is a striking uniformity in the history of most cases of sprue. On inquiry, we shall probably learn that the patient has been suffering for months, or perhaps years, from irregularity of the bowels. This, we may be told, began soon after arrival in the tropics as a bilious morning diarrhœa. For a long time this morning diarrhœa went on, without interfering in any way with the general health. Later, the mouth, now and again, became tender, little blisters or excoriations appearing for a day or two at a time about the tip of the tongue or inside the lips. These sore spots would come and go. Perhaps, from time to time, exacerbations of the mouth symptoms would be associated with a little increase of diarrhœa. Gradually the stools lost their bilious character and became pale and frothy; dyspeptic symptoms, particularly distension after meals, now appeared. As time went on, these symptoms would recur more frequently and in a more pronounced form, following, almost inevitably, any little imprudence as regards food or exposure. The general condition now began to deteriorate; emaciation, languor, lassitude, and inability to get through the day's work satisfactorily becoming more pronounced each summer until, finally, a condition of permanent invalidism was established. Should the disease continue to progress, the emaciation advances slowly but surely. Diarrhœa may be almost constant, and now no longer confined to the morning hours; the complexion becomes dark, sometimes very dark; the appetite, sometimes in abeyance, is more frequently ravenous, unusual indulgence in food being followed by increased discomfort, temporarily relieved by smart diarrhœa. At length the patient is confined to the house, perhaps to bed. The feet become œdematous, and the integuments hang like an ill-fitting garment, the details of the bony anatomy showing distinctly through the dry, scurfy, earthy skin. Finally the patient dies in a semi-choleraic attack; or from inanition: or from some intercurrent disease. Such is the history of an ordinary, mismanaged case of sprue.

Another type of case commences as an acute entero-colitis or hill diarrhœa, with sudden and profuse colicky diarrhœa, perhaps vomiting, and a certain amount of fever. The acute symptoms do not subside completely, but gradually have the typical symptoms of sprue grafted on to those of an acute intestinal catarrh.

Incomplete sprue. (*a*) *Gastric cases.*—Occasionally we meet with cases of confirmed sprue in which the morbid process is at first, judging from the existing clinical symptoms and subsequent history, confined to a limited part of the alimentary canal. Thus we sometimes get

sprue without diarrhœa, the principal symptoms being sore mouth, dyspeptic distension, pale, copious, but solid stools, and wasting.

(*b*) *Intestinal cases.*—On the other hand, we may get cases in which the mouth is not eroded and there is little or no distension or dyspepsia, but in which the stools are liquid, copious, pale, and frothy. Sometimes a patient, who may have suffered at an earlier period or on a former occasion from the first type of the disease, later acquires the diarrhœic form; and *vice versa*.

(*c*) *Sprue without diarrhœa.*—It sometimes happens that under treatment the sore mouth, dyspepsia, and diarrhœa completely subside; nevertheless, the wasting continues, the stools remaining phenomenally copious—so much so that the patient may declare that more is passed than has been eaten. In this case wasting is progressive, and the patient gradually dies of inanition.

(*d*) *Tongue or mouth sprue.*—As a rule the characteristic appearance of the tongue is associated with gastric and intestinal symptoms, but this is not invariable. The Editor originally described three cases in Ceylon and he has seen several others during the last fifteen years. This process may remain confined to the mouth and gullet for two years or more before the typical intestinal symptoms are noted.

Intestinal atrophy consequent on sprue.—In certain instances, under treatment the symptoms proper to sprue subside; but the patient's digestive and assimilative faculties are permanently impaired. Slight irregularities either in the quality or the amount of food, chill, fatigue, depressing emotions, and other trifling causes suffice to bring on dyspepsia accompanied by flatulence and diarrhœa. These cases may linger for years. Usually they improve during the summer in England, getting worse during the winter and spring, or during cold damp weather. Ultimately the patients die from general atrophy, diarrhœa, or some intercurrent disease.

Sequelæ. *Anæmia and spinal symptoms.*—Severe anæmia of the pernicious type is a frequent sequel (*see* p. 575), and until recently it had been generally considered that sclerosis of the spinal cord did not eventuate in sprue and served to distinguish it in some degree from subacute combined degeneration of cord type seen in Addisonian anæmia. In the Editor's opinion no such distinction can be substantiated, for in two longstanding cases of sprue with severe anæmia, he observed the advent of unmistakable signs of cord involvement—in spastic paraplegia, ankle-clonus, positive Babinski signs, and eventually complete and fatal paralysis of the lower extremities. There was nothing in these cases to differentiate them from other cases of subacute combined degeneration. Neuritic signs in the arms and legs (pins and needles) are frequently observed; sometimes also actual *neuritis* of the legs, with paræsthesia and loss of reflexes, resembling beriberi, which has been found to respond satisfactorily to vitamin B_1 therapy.

Œdema.—A generalized œdema, especially of the legs, is a frequent

accompaniment of sprue, especially in those cases who are responding well to treatment. This is usually regarded as due to water-retention by the tissues and is on the whole a favourable sign.

Purpuric rash.—In two cases the Editor has observed a petechial hæmorrhagic rash specially noticeable on the thighs and legs (Fig. 55). This is undoubtedly a scorbutic phenomenon and occurred in cases who had been fed on a prolonged milk dietary. The rash rapidly disappeared after the administration of adequate amounts of vitamin C. Small subcutaneous hæmorrhages on the hands are common in atrophic cases of sprue and are indicative of vitamin C deficiency.

Dermatitis.—A peculiar form of rash, a very irritable dermatitis, is a frequent accompaniment of sprue, especially in elderly people with extreme anæmia. This dermatitis generally breaks out during convalescence and when the patient is responding to treatment. It is mostly seen on the arms and chest. It may possibly be *pellagrous* in nature. The Editor has recorded one remarkable case of the association of a pellagrous rash with sprue, in which immediate improvement occurred on the administration of nicotinic acid. Similar manifestations have been recorded in cœliac disease and in idiopathic steatorrhœa.

Latency.—One of the most remarkable things about sprue is the latency of the process. The disease may arise in England in persons who have at some time resided in an endemic area of the disease: usually this period is one or two years; sometimes it is longer—seven or eight years; exceptionally the latent period may be as long as twenty-five.

Diagnosis.—The condition of the tongue, the character of the stools, and the history are sufficiently distinctive, one would suppose, to render diagnosis an easy matter. Nevertheless, we have known of cases in which the disease has been diagnosed and treated as syphilis, the condition of the mouth being attributed to this disease, and the character of the stools and other symptoms being ignored. Care must be exercised in interpreting the significance of the small area of liver dullness usually found in well-marked cases of sprue. This is not due to cirrhosis of the liver, but to the wasting the liver undergoes in common with the soft tissues of the entire body.

Cœliac disease (Gee's cœliac diarrhœa, or the Gee-Herter syndrome) occurs frequently in Europe in children under ten years of age, and is also seen in those of European parentage returning from the tropics. The ætiology of cœliac disease is probably different from that of sprue, but the stools are very similar in appearance and in chemical composition. This disease is associated with diarrhœa and meteorism, stunted growth, and incomplete sexual development. There is no involvement of the tongue and mouth, and the anæmia is not so severe as in sprue. Symptoms usually disappear on placing the small patients on a fat-free dietary. *Idiopathic steatorrhœa* is probably the same process as cœliac disease persisting in adult life, and is apparently the disease described by

Thaysen in Denmark and Northern Europe as *non-tropical sprue.* This is a nutritional disturbance associated with tetany, osteomalacia and anæmia. It is characterized by disturbances of the calcium metabolism and hypochromic anæmia. According to the views of Bennett, Hunter, and Vaughan, in "*non-tropical sprue*" there is often severe anæmia, various cutaneous lesions, infantilism, megacolon, fine silky hair, brittleness and ridging of the nails, and a flattened type of blood-sugar curve after ingestion of glucose (which is also found in sprue). *Lens opacities*, gross bony deformities, and tetany constitute the outward signs of defective calcium metabolism. The serum calcium is low and there is excessive excretion of fat. Both cœliac disease and idiopathic steatorrhœa may be complicated by secondary pellagra.

The absence of skin lesions and mental symptoms differentiates sprue from *pellagra*. Difficulty may be experienced in differentiating the sprue tongue from that of pellagra; in the latter disease it is pointed, and when it is inflamed and painful the process is found to be generalized over the whole organ, and not confined to certain definite and circumscribed areas as in sprue, and there is ulceration at the angles of the mouth. The tongue of early B_6 avitaminosis, as originally described by the Editor in Ceylon, is associated with angular stomatitis and an atrophic condition of the lips (perlêche). It is apparently identical with the pellagra tongue, and amenable to treatment with nicotinic acid. It is necessary to remember that atrophy of the lingual papillæ occurs in pernicious anæmia and even in malarial anæmia and ancylostomiasis—diseases which may be confused with sprue. No difficulty should be experienced in differentiating *Addison's disease* from sprue. A *gastro-jejuno-colic* fistula may cause symptoms closely resembling sprue. Kilner and Fairley have described three cases with glossitis, fatty diarrhœa, and anæmia, in which previous gastro-enterostomy had been performed.

According to Thaysen the low blood-sugar curve after the intake of 1 grm. of glucose per kilo body-weight serves to differentiate sprue from pernicious anæmia and allied conditions, but a similar curve accompanies idiopathic steatorrhœa and cœliac disease. *Lambliasis* or *giardiasis* (*see* p. 567) may produce white fatty stools and fatty diarrhœa, and the Editor has seen cases of this condition mistaken for sprue.

The differentiation of sprue from chronic pancreatitis may present difficulties. In the latter condition the neutral fats predominate in the fæces, the tongue and mouth are not involved, and the diastatic reaction of the urine is high. The anæmia of sprue greatly resembles that of true Addisonian anæmia, though normoblasts are rare in the blood of sprue and megaloblasts do not occur. High van den Bergh readings are the rule in true pernicious anæmia: exceptional in sprue. The differentiation from tropical macrocytic anæmia or nutritional anæmia cannot be easily made on blood examination alone, as the picture is very similar. It specially affects pregnant women in the

tropics, and is not accompanied by diarrhœa. Certain cases of tabes mesenterica may, on clinical grounds, resemble sprue, and so may malignant disease of the mesenteric glands, such as lymphosarcoma.

The radiographic findings in sprue.—According to the Editor's experience and that of Pillai and Murthi, in acute incipient cases there is no loss of tone in the stomach or intestines. The stomach is emptied in two hours after the barium meal, the hepatic flexure of the colon is reached in three hours, and the intestines are empty in 6–8 hours. In subacute cases there is slight loss of tone and vigour of peristalsis of stomach. In chronic cases there is ballooning of the large intestine with some delay in the cæcum and colon.

Prognosis is good for recent cases, provided proper treatment is carried out. It is bad for patients over fifty, for longstanding cases, for careless and injudicious patients, and for those who cannot or will not take a special diet.

Treatment

General statement.—The treatment of sprue is mainly a matter of bodily rest and careful dieting in order to procure assimilation of the most easily absorbable foods. If treatment be undertaken sufficiently early, and be thoroughly and intelligently carried out, it is generally marvellously successful. Should, however, it be undertaken at too late a period, when the glands and the absorbing surface of the alimentary canal have been hopelessly destroyed, do what we will the case is almost sure to end fatally. In prescribing treatment, therefore, the first thing for the physician to do is to get his patient thoroughly convinced of the deadly nature of his complaint; for, unless he receives the patient's hearty and complete co-operation, he must not expect to cure a well-established case. To be successful, treatment must be thorough, sustained, and prolonged. All predisposing causes, as uterine or other discharges, syphilis, scurvy, and the like, must, of course, be dealt with and, so far as possible, removed. The size and weight of the fæces should be estimated daily by weighing the pan and subtracting from the total the known weight of the receptacle. The average daily weight of normal fæces is from six to eight ounces; in sprue it is commonly double or treble this. By keeping a chart of the average daily excretion, and by estimating the weight of the food ingested, an estimate may be formed of the daily intake and output.

The nursing of sprue cases is all-important. A great deal rests with the nurse; sprue patients are apt to be unreasonable and refractory, so she will need to be sympathetic and tactful, yet firm. A regular routine of feeding should be adopted and strictly adhered to both in quantity and ingredients.

The sheet anchor of treatment in sprue is diet, and to this principle all who have written on this disease unanimously subscribe This is an

exceedingly difficult subject to write about, because what suits one individual case may not by any means suit another. Individual patients seem to thrive on the most widely diverse diets. Some patients, even at the present day when more tolerant ideas are held, may thrive on the old-fashioned milk dietary.

In prescribing a dietary for sprue the principle should be borne in mind that the two main ingredients of a mixed dietary—fats and starches—are incapable of being digested or assimilated. As the true ætiology of sprue remains at present in such an uncertain state, it is small wonder that many individual preferences for different lines of treatment exist, and the Editor has thought fit to give preference to that particular mode which in his experience has been found most helpful.

Dietetic treatment No. 1.—The Editor is of the opinion that a combination of the milk and protein dietary meets the needs of most cases. If the tongue be very sore and the intestinal symptoms urgent, the case is fed for the first week on a milk dietary (*see* p. 586) and, if this is not easily tolerated, the high protein-containing milk—Sprulac (*see* p. 585). Sometimes, however, a mixture of milk and Sprulac may be resorted to, or a diet of Benger's, Horlicks, or "Almata." Where the intestinal symptoms have subsided other ingredients may be added, as set out in the following tables:

Table I

First week.

Three pints of cow's milk (or Benger's Food) daily in 5-oz. feeds at two-hour intervals.

Toast, "pulled bread," "Heudebert" rusks with a small quantity of butter.

Total calorie value, about 1,100 calories.

Table II

Second week.

Three pints of milk (or Benger's Food) daily as in Table I.

Rusks (Heudebert's or Verkade's "Groote Beschuit") and toast. Sago, 6 oz.; liver soup, 12 oz. in two feeds of 6 oz. each.

One lightly boiled egg.

Weak tea or sprue tea (i.e. tea infused with milk in place of water) 8 oz.

Total calorie value, about 1,900 calories.

Table III

Third week and during convalescence.

Breakfast.—Porridge; 1 egg; toast (or rusks) and weak tea.

11 *a.m.*—Half a pint of warm milk, Sprulac, or Benger's Food.

Lunch.—Liver soup, 12 oz.; chicken (minced), 6 oz.; spinach, 3 oz. (or cauliflower, or French beans, or vegetable marrow, 3½ oz.); sago or semolina pudding, 6 oz.; baked apple or banana, 6 oz.

Tea.—Toast; tea; Madeira cake, sponge cake, digestive biscuits (McVitie and Price), 3 oz.

Dinner.—Brain or sweetbread, 4 oz.; calves'-foot jelly, 3 oz.; banana, 3 oz.; arrowroot, 8 oz.
Total calorie value, about 3,900 calories.

The diet as set forth is given during the first week and must be continued with the various simple medicinal measures which are enumerated in this section; naturally it can be varied according to the needs and idiosyncrasies of each individual patient. The third table is instituted from the third week onwards and during convalescence for at least three or four months. It may be varied, of course, according to circumstances, and during the fruit season strawberries and raspberries may be added to the regimen.

In elderly patients (*i.e.*, those over 45 years of age) and where there is a high degree of anæmia, the addition of raw or underdone, finely shredded beef is of advantage.

Minced Beef for Sprue Patients

8 oz. best beef;
1 good teaspoonful of marmite;
Pepper and salt;
2–3 tablespoonfuls of water.

Trim off all fat from the beef. Mince the raw beef finely, putting it twice through the mincing machine if necessary.

Calorie value of 4 oz. is about 188.

Place in double saucepan with marmite, seasoning, and water. Cook over boiling water, *stirring the ingredients with a fork all the time* until the meat has turned *brown and crumbly*—roughly 3 minutes.

Serve on a hot-water plate. Treated in the above manner, minced beef is a palatable dish.

In those patients with flatulency and meteorism which are increased by milk, this beef diet may be substituted for one pint of milk.

Lightly-steamed meat with the addition of gravy is advantageous. This should be steamed in the following manner:

Take undercut of beef, 4 oz. Steam with 6 oz. of water for 5 to 7 minutes. Add a pinch of salt and serve as a sort of thick soup with lemon juice or slice of tomato.

The recipe for liver soup is as follows:

Take half a pound of calves' liver and cut it into small pieces. Place it in a double saucepan, add ½ pint of cold water and simmer for 1½ hours. Strain through a sieve and add 1 pint of bone stock or chicken jelly, and, if necessary, flavour with marmite. Add a small quantity of pepper and salt.

Liver soup can be given in soup-platefuls of 8 oz. each, and may be taken together with underdone meat.

These methods of treatment—followed by a carefully selected and increasing mixed diet, combined with warmth and rest—are the most successful ways of dealing with sprue. Nevertheless, we have seen cases in which, after failure of the most carefully carried out milk or

protein diets, a mixed diet proved successful for a time. In such mixed diets, in fact in all diets in sprue, *restriction in the amount* is as important, perhaps, as the nature of the food consumed. Food should never be given unless the patient is hungry. It is a great mistake to try to make these patients fat rapidly, or to stimulate the desire for food by encouraging active exercise. The bowel is not in a condition to deal with large meals.

Dietetic treatment No. 2. *High-protein dietary.*—Especially in elderly patients with inadequate assimilation, hypochlorhydria and great anæmia, the high-protein dietary is indicated. In 1906 Cantlie introduced the meat dietary in sprue. His ideas were based originally on the Salisbury treatment, and were specially devised for those unable to take milk. A high-protein dietary suitable for sprue patients with advanced anæmia and in whom flatulency and meteorism are pronounced features, has been introduced. Alimentary rest in these cases is the therapeutic ideal and this can be attained by feeding the patient with a minimum amount of those food constituents which the small intestine fails to deal with adequately. Protein is the chief constituent of the diet, commencing with a low-calorie value and gradually increasing the quantity while maintaining the high-protein rates. During this treatment five diets are ordered, the calorie value of which increases progressively from 770 in No. 1 to over 3,000 in No. 5, and the ratio of protein to fat carbohydrate is maintained at 1·0 : 0·3 : 1·1.

Diet No. 1 (Calories 770).

8 *a.m.*—Underdone beef, 3 oz.; juice of half an orange and glucose, 2 drachms.

12 *a.m.*—Soup, 4 oz.; underdone beef, 3 oz.; rusks, ¾ oz.; juice of half an orange and glucose, 1 drachm.

6 *p.m.*—Same as above.

Diet No. 2 (Calorie value, 1,200).

The underdone beef is increased to 5 oz., and rusks and calves'-foot jelly added at 4 p.m. Tea, 10 oz.

Diet No. 3.—Meals are given from 6 a.m.–7 p.m., as follows: 6 a.m., 8 a.m. 10 a.m., 12 a.m., 4 p.m., 7 p.m. The diet is much the same, with the addition of 10 oz. of tea with milk, three times daily, two baked apples and calves'-foot jelly.

Diets 4 and 5.—The times are the same, but a greater quantity, up to 7 oz. of underdone beef is given twice daily. Bananas, custard and honey are introduced into the diet.

High-protein milk treatment.—As the result of biochemical investigations, it is now held that flatulency and abdominal discomfort is in the main aggravated by the proportion of fat in cow's milk. Fairley has advocated a milk powder which combines the advantages of a high protein dietary with the bland properties of milk. In consequence a high-protein milk powder known as *Sprulac* (Cow & Gate Ltd.) has been manufactured. This powder is prepared from fresh milk which

has been treated by passage through a gauze and wire filter, subsequently chilled, centrifuged to get rid of organic and inorganic debris, passed through a mechanical mixing apparatus and desiccated at 120° C. The powder contains 10·6 per cent. fat; 34·0 per cent. of protein and 45·0 per cent. of lactose. The calorie value per ounce is 125 and the ratio of protein, fat and carbohydrate is 1·0 : 0·3 : 1·3. Sprulac can be given in the same manner as milk in milk treatment. One ounce of Sprulac is made up to 8 oz. with water and given every 2½ hours for six feeds. Subsequently the amount may be increased and calves'-foot jelly and the juice of two oranges added.

Dietetic treatment No. 3. *The milk treatment.*—In the days of Manson and Thin the milk treatment of sprue was found to be very successful, and certainly the sensational results that sometimes followed this treatment appeared to justify the faith that was placed in it. The essence of the treatment resided in the assimilation of a bland, highly nutritious, easily digestible, and absorbable fluid. Although many critics at the present day will be found to oppose this treatment on biochemical lines, yet to the sprue patient with his raw and extremely sensitive mouth and his painful gullet, milk will sometimes appear to be the only food which can be swallowed and assimilated in the acute stage of the illness. There are those to whom the taste of milk is unpalatable, and there are others who possess an idiosyncrasy against it and in whom the ingestion of milk gives rise to severe digestive disturbances. Besides which, a milk dietary is extremely monotonous and it takes a rigid will to carry out the treatment in its entirety. The objections to the high fat-content of milk and its effect upon digestion have been dealt with under *Sprulac.*

In carrying out milk treatment it is well to commence with a dose of some aperient—castor oil or pulvis rhei compositus. Pending the action of the drug, all food, including milk, should be withheld. The patient should be sent to bed in order to economize strength and maintain equable warm temperature of the skin. He should also be directed to clothe warmly, to encircle the abdomen with a broad flannel binder, to cover his arms and shoulders with a warm jacket, and to live in a large, sunny, warm room. At first 70 oz. at most are allowed in the twenty-four hours, eight-ounce feeds being given every hour or every two hours. When the patient is very weak the feeding must be continued during the night. *The milk should not be drunk, but sipped with a teaspoon, or taken through a straw or a fine glass tube, or from a child's feeding-bottle.* As a rule, on this regimen, in the course of two or three days, the patient's condition is very much improved. The stools have increased in consistence—are solid, perhaps—the distension of the abdomen has subsided, dyspeptic symptoms have vanished, and the mouth is much less tender and less inflamed. The quantity of milk should now be increased at the rate of half a pint a day or every second day, until 5 pints, or thereabouts, are taken in the twenty-four hours. It is well to keep at this quantity for ten days at least, when, everything going well, a gradual increase to 6 or 7 pints may be sanctioned. If the patient gets weary of milk, Benger's food forms an efficient substitute. Very often patients prefer this to milk, and, in order to vary the monotony, it is often wise to give it in alternate feeds with pure milk. Being predigested, Benger's food is particularly well borne by sprue patients; moreover, the preparation is palatable. Some patients, unable to tolerate milk, thrive on "Almata"

or "Horlick's." Up to this point the patient should keep in bed; but when he is able to take 6 or 7 pints of milk he may get up and, if he feels strong enough and the weather is mild, go out of doors. *For six weeks, dating from the time the stools become solid and the mouth free from irritation, no other food or drink whatever should be permitted.* A raw egg, if it is found to agree, may now be added to the milk; later, some artificial malted food; next, small quantities of well-boiled arrowroot, rusks, pulled bread, thin bread (stale) with a little butter, or some digestible form of biscuit; later still, chicken broth, and a little fruit; and, by and by, fish and chicken may be gradually introduced. To some patients the milk is made more palatable by the addition of a pinch of salt to each glass. A. Stephens has suggested oxygenating milk by means of oxygen "sparklets."

In commencing this treatment, if the patient, after two or three days, be found unable to digest and assimilate so much as 3 pints of milk in the twenty-four hours, the daily allowance must be reduced by half a pint a day until only 30 oz. or thereabouts are taken. If now the motions become solid, the quantity of milk may be gradually increased by 5 or 10 oz. a day, so that in the course of a few weeks the full allowance—6 or 7 pints—is consumed. In cases with persistent dyspepsia, pancreatic preparations, such Savory & Moore's pancreatic emulsion, or taka-diastase may be of benefit. Milk may occasionally be made more digestible and tolerable by the addition of bovril in the proportion of one teaspoonful to every 8 oz., or by being beaten up with the yolk of an egg. Marmite, given in teaspoonful-doses dissolved in water or milk, is occasionally of benefit.

Usually in milk treatment the fæces become hard and scybalous, and the patient suffers much from distension. In these circumstances castor oil, in drachm-doses, should be given in liquid form or in cachets. As a general rule, this immediately relieves the condition. The routine administration of medicinal paraffin in teaspoonful doses is sufficient to keep the motions from balling. *Petrolagar*, or *agarol* (preparations of liquid paraffin and agar), given in teaspoonful to tablespoonful doses, are also particularly suitable for sprue patients. Flatulency is best counteracted by small doses of castor oil, by hot baths, and by restricting the amount of food.

Dietetic treatment No. 4. *Fruit treatment.*—The value of fruit in the treatment of sprue and other forms of intestinal disease has long been recognized by practitioners. Manson was in the habit of prescribing bananas and apples, tentatively, of course, in sprue, and often with marked success. Of late, repeated trials of the strawberry in sprue have confirmed one's personal belief in the value of this fruit treatment, and in the strawberry treatment in particular. The plan Manson followed was to give one or two strawberries with each feed of milk, and, if found to agree, to increase the number gradually until 2 to 3 lb. were taken daily. Bottled fruits, particularly peaches and pears, make suitable substitutes if strawberries or bananas are not obtainable. Of the tinned fruits the most suitable are Libby's strawberries and blackberries, though it is doubtful whether preserved fruit possesses the same virtues as fresh in this disease. Fresh raspberries and blackberries, when eaten in the same way, are almost as well tolerated as are strawberries. A dietary of fresh tomatoes is often beneficial. The bael fruit or Bengal quince (*Ægle marmelos*), introduced by Fayrer in the treatment of this disease, seems to exert a very beneficial effect in the countries (Ceylon and India) where it can be procured in a fresh state; during recent years it has been imported from the East on ice, and offered for sale in London.

The ripe pulp should be scraped out of the hard exterior shell and eaten raw with sugar and cream, or made up with gelatin in the form of a jelly. Two or three of these fruits, depending on their size, may be given every day. Extracts of bael fruit (*Extractum belæ liquidum*), such as are frequently sold in England, appear to be quite inert, but there is an efficient bael-fruit paste which can be procured from the U.P. Stores, 15, Lindsay Street, Calcutta.

When to send the patient to Europe.—When sprue develops in the tropics, if feasible the patient should be sent to Europe as soon as possible. It is a mistake, however, to ship an invalid if the disease is active, or if his end is manifestly not very far off. Diarrhœa should not be active when the patient is put on board ship. In every case, provision, such as a cow or an abundant supply of suitable milk, should be made for carrying on treatment during the voyage.

The clothing and general management.—Sprue patients returning to Europe ought to be especially careful in their clothing, and they ought to get out their warm clothes before the ship leaves the tropics. If their return is during the winter, they should arrange to remain in the south of Europe till at least late spring. Next to an unsuitable dietary, perhaps cold is the most prejudicial influence to which a sprue case can be exposed. A sprue patient ought never to feel cold; he ought always to wear thick flannels, thick stockings, and, when up and about, thick boots. In winter a chamois-leather waistcoat provided with sleeves is of great service. His rooms ought to be warm. He ought to eat very sparingly. He ought never to be fatigued; he ought to go to bed early and rise late; in fact, he ought to do everything in his power to avoid irritating the bowel, to guard against chill, physiological depression, and the necessity for copious eating.

During the summer England is suitable enough as a residence; but during the cold winter and spring months some milder, drier, and more sunny climate must be sought out.

Drug treatment of special symptoms.—Experience soon teaches one to distrust medicines in sprue. Occasionally a gentle aperient is of service, or, if diarrhœa is watery and excessive, a few drops of laudanum; but active drugging of all sorts is, as a rule, prejudicial.

Sore tongue and mouth.—A great deal can be done to ameliorate the soreness and the dysphagia caused by ulceration of the tongue and mouth. The mouth should be kept very clean and washed out after each feed with a bland mouth-wash such as potassium chlorate 1 drachm to the pint of hot water, but if the mouth is very painful, cocaine 2 gr. to the ounce of glycerin and borax, brushed on to the tongue lightly before eating, will deaden sensibility. In certain cases where the saliva is very acid, as it generally is when the tongue is very raw, an alkaline mouth-wash should be used as follows:

Sod. bicarb.	gr.x (0·648 grm.)
Sod. biborate	gr.x (0·648 grm.)
Rose-water	℥iv (113·6 c.c.)

Diluted with water according to taste.

Phillips' Milk of Magnesia—1 teaspoonful to half a tumblerful of water—is also useful.

The most efficient solution for healing the mouth lesions—and its action is sometimes astonishingly rapid—is an acriflavine dye, *Glauramine* (B.D.H.), of which the mouth-wash is made up of one teaspoonful (one drachm) to eight ounces of warm water. It stains the mouth and lips yellow, but this is only a temporary effect. In some cases, especially where there is sepsis, hydrogen-peroxide mouth-wash is useful. *Lavoris mouth-wash* (Lavoris Chemical Co., Toronto), 1 part to 2 parts of water, is also recommended. To take away the soreness and pain there is nothing better than *Euphagin* tablets (paramido-benzoic ethylester with menthol and sodium borate). The Editor has recently observed, in cases in which the tongue and mouth lesions with angular stomatitis dominate the clinical picture, a remarkable improvement takes place on *nicotinic acid* 150–300 mgm. daily. The sense of taste and smell return with greater celerity and to a more complete extent than with any other method. Nicotinic acid in acute cases is given in a dosage of 300 mgm. daily. The tongue lesions appear to heal as rapidly as in the analogous case of pellagra, while one of the most striking features is the change in the appearance of the fæces, which assume the dark and normal fæcal colour within a period of a few days.

Anorexia and vitamin B_1 deficiency.—The loss of appetite and taste in severe cases of sprue is a difficulty, but it usually improves gradually when the patient is put to bed. It has been found that vitamin B_1 increases the desire for food in experimental animals, so that the author has recently injected vitamin B_1 [1] in ampoules containing 2 mgm. of crystalline vitamin daily. It is also curative in those cases of sprue presenting neuritic symptoms.

Petechial hæmorrhages and scorbutic symptoms.—The Editor has treated two with a purpuric rash resembling that of scurvy, and this tendency calls for administration of vitamin C, in the form of either ascorbic acid, or orange juice.

Sprue with secondary pellagra.—In a chronic case from Hong Kong which developed the skin manifestations of pellagra, the Editor administered nicotinic acid (150 mgm. daily for ten days, and thereafter 50 mgm. daily for six weeks) with successful results. The total increase of weight after a period of three months was 41 lb.

Diarrhœa.—The diarrhœa of sprue yields to dietetic treatment, but if excessive the best method is to administer a small quantity of castor oil in teaspoonful doses, after which Batavia powder in teaspoonful doses should be given, suspended in milk or water. If the nocturnal diarrhœa is very severe, *chlorodyne* (10–15 min.) is often successful.

Batavia powder is a modification of "Peter Sys" specific (Shanghai) which was originally used by Manson and Cantlie in China. Batavia powder

[1] Benerva (Roche) and Betaxan (Bayer).

is cuttle-fish bone combined with an iron compound. In some cases of diarrhœa during convalescence, it is advantageous to give it in wafer cachets, 15 gr., four times daily.

In diarrhœa of a less obstinate character, Crooke's Collosol Lacto-Kaolin, in doses of one drachm daily, is also to be recommended, while on occasions a bismuth and magnesia mixture (bism. oxycarb. 15 gr., mag. carb. pond. 15 gr.) with sp. chlorof. et morph. co. may be considered more suitable.

Flatulency and meteorism.—Persisting flatulency and meteorism are usually connected with some unsuitable element in the dietary, and in a mixed dietary it may be due to the milk employed. In cases of extreme distension the injection of pituitary extract, especially *pitressin* (½–1 c.c.), is followed by the passage of flatus and instant relief. Tablets of salol (10 gr.) are also useful. Then there are the charcoal preparations, such as charcoal biscuits or Charkaolin (Allen and Hanbury) in teaspoonful doses. The following prescriptions may also be used :

Spirit. æther. nitros. . . .	♏xv (0·88 c.c.)
Spirit. ammon. aromat. . .	♏xv (0·88 c.c.)
Aq. menth. pip. ad . . .	℥ss (14·21 c.c.)

or

Ol. menth. pip.	♏xvi(0·94 c.c.)
Mag. carb.	ʒi (3·89 grm.)
Cret. prep.	gr.x (0·64 grm.)
Sod. bicarb.	ʒi (3·89 grm.)

Fiat pulv. 1 teaspoonful in ℥ iv of water.

In some cases a combination of pituitary therapy combined with high colonic lavage with hypertonic saline (2 pints) gives relief when other measures fail.

Constipation.—The constipation following the acute phase of sprue may be difficult to overcome. Often hard scybala form in the sigmoid colon and become impacted there. The best aperient is castor oil. In extreme cases it may be necessary to give an enema of warm olive oil (10 oz.) and to remove the scybala from the rectum by means of the finger. As a general aperient, petrolagar (*red label*) is useful, as is also agarol, preparations which have superseded liquid paraffin. Isogel (Allen and Hanbury) a new preparation given in doses of several drachms, may also be used.

Anal excoriation and irritation is sometimes a distressing feature, and may be relieved by the following ointment :

Orthoform	40 gr.
Zinc oxide	120 gr.
Starch	120 gr.
Paraffin . . . . ad	1 oz.

Tetany and cramps.—The treatment of the states due to calcium deficiency is met with by the administration of calcium by the mouth in doses of 10 gr. three times daily, and in extreme cases by intravenous injection of calcium salts, such as calcium gluconate (Sandoz) 10 c.c. or more. *Scott's treatment* consisted of exhibiting calcium lactate in doses of 10 gr. three times daily, together with tablets of extract of parathyroid (Parke Davis) $\frac{1}{10}$ gr., two at night. This treatment was continued for six weeks, and it was found that this method is of considerable benefit to those patients in whom calcium deficiency is a feature.

To increase assimilation.—Glucose, 2 oz. daily, should be added to the dietary throughout, and to increase assimilation in those cases in which intestinal atrophy is a feature, *insulin* from 2–6 units, injected twice daily, may often be followed by an increase of the appetite and a corresponding aptitude for absorption.

Anæmia of sprue.—In extreme cases no advance in the treatment of sprue has been so remarkable as blood-transfusion in those cases in whom the anæmia has become so extreme as to resemble the most desperate forms of Addisonian anæmia. In the original cases described by the Editor, this measure appears to have been a cure, not only for the anæmia, but for the underlying sprue. Some cases with a red cell count of 500,000 red cells to the c.mm. have entirely recovered. All special precautions as regards blood grouping must be taken, and 300–400 c.c. of citrated blood injected intravenously. Sometimes two or three transfusions at weekly intervals are necessary to restore the functions of the bone-marrow.

The beneficial effects of liver soup in sprue have been noted since the early days of Manson and van der Burg, and since the work of Minot and Murphy in 1926 it has been customary to strengthen it by the addition of more potent liver extracts. The best are those of Eli Lilly, Parke Davis, and Liveroid (Oxo), but large quantities are required and they are expensive. An important advance has been made in the intramuscular injection of liver extracts. In the Editor's hands, *Campolon* (Bayer), *Hepatex*, and *Examen* have been most efficient. In grave cases 6 c.c. are injected daily for six injections, but usually a series of 12 injections of 2 c.c. each suffices. Where these larger amounts are well tolerated, injections of 10 c.c. each given three times weekly have proved to be beneficial. The injections should be made deep subcutaneously in the region of the buttock, and is usually followed on the ninth or tenth day by a remarkable rise in the reticulocyte count. The first injections may be rather painful at the site of inoculation, but this gradually works off as further ones are given. This method has the added advantage of being cheaper than other forms of liver therapy. Sometimes the addition of iron is of advantage, especially in those cases without megalocytic blood changes. It may be given in the form of ferrous sulphate tablets (Glaxo) three times daily, or *hæmatinic plastules* (Wyeth).

Achlorhydria.—In those forms of sprue anæmia associated with achlorhydria, the treatment should be instituted on the same lines as for pernicious anæmia. In the severe forms, dilute hydrochloric acid 20–30 min. in orange juice is given with the meals, and in some cases appears to check the diarrhœa, but when the tongue and mouth are very sore, hydrochloric acid in solution increases the pain. In these cases tablets of acidol-pepsin (Bayer) two to three times daily, should be given instead.

Additional subsidiary methods of treatment.—Massage and passive movements are of benefit, especially in men who have been accustomed to exercise. Massage of the arms and legs should be practised to commence with, but the abdomen should be deferred till after the more urgent symptoms have subsided, when in constipated cases it is of distinct value.

Heliotherapy and ultra-violet light radiations to chest and abdomen are of very stimulating value during convalescence in atonic and debilitated cases.

Dermatitis.—The very irritating dermatitis which is frequently observed in elderly patients who are responding well to treatment, is difficult to cope with. The Editor has seen the best results from a preliminary course of calamine lotion followed by the application of a pigment containing cignolin 4 gr. and oil of cade (deod.) 40 min. to benzoli rect. one ounce. A glycerine and ichthyol lotion is also very useful.

Convalescence.—The sprue patient, if possible, ought not to return to the tropics. If compelled by circumstances to do so, he must exercise the utmost care with regard to his health, and avoid exposure, cold baths, and all excesses; take a minimum of cooked meat, unless specially prepared; purge gently, and go on absolute simple diet on the slightest sign of relapse. Alcohol, especially strong spirits, is strictly contra-indicated for at least three months from the time of apparent recovery; light French wine may then be permitted.

Appended is a diet table which should serve as a guide for convalescent cases of sprue, and which should be continued as long as possible.

Suggested Diet for Convalescent Cases of Sprue

Breakfast.

- Well-boiled porridge (Quaker oats) or gruel. Sour milk (yoghourt).
- Lightly boiled egg.
- Toast, rusks or biscuits (Energen bread or Heudebert rusks).
- Cocoa, weak tea,[1] or chocolate made with milk.
- Butter in small quantities with toast or rusks.

11 *a.m.*

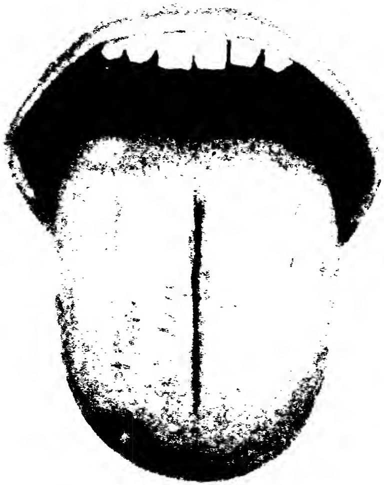
Warm milk or Sprulac, half a pint.

Lunch.

- Clear, or liver soup, or chicken broth.
- Chicken, preferably minced, boiled or roast.
- Underdone minced beef.
- Spinach, vegetable marrow, young peas, cauliflower, or French beans.
- Well-cooked milk puddings: sago, semolina.
- Baked apple or baked banana.

[1] Sprue tea is best made with boiling milk in place of water.

Avitaminosis (B2) tongue prepellagrous, showing angular stomatitis.



Acute stage of sprue with typical aptha.

Chronic sprue tongue

PREPELLAGROUS AND SPRUE TONGUES.

PLATE XX

EARLY MACULAR RASH OF LEPROSY

Suggested Diet for Convalescent Cases of Sprue—continued

Tea.

Weak tea.
Toast.
Wafers, water or Marie biscuits.
Madeira cake.
Heudebert rusks.
Sponge fingers.

Dinner (7 *p.m.*).

Brains.
Sweetbread.
Fruit or calves-foot jelly.
Arrowroot.
(*Dinner should be the lightest meal of the day.*)

Fruits permitted.

Bael fruit, bananas, oranges, papaya, tomatoes.
Ripe pears.
Apples occasionally, preferably baked.
Strawberries, commencing with ½ lb.; maximum, 3 lb.
Raspberries, blackberries (as above).
Hot-house grapes.
Fruit jellies.
Preserved fruit, especially peaches and pears.

Articles of diet to be avoided.

Salmon, trout, mackerel, herrings.
Cheese.
Fresh bread.
Jams, especially marmalade.
Grease or fat.
Suet puddings.
Nuts.
Cakes with raisins.
Potatoes in jackets or fried.
Pastry of all kinds.
Alcoholic drinks, especially spirits—gin, brandy and whisky.
Mineral waters.

Treatment of complications.—Careful search should be made for any coexisting infection from which the patient may be suffering and which is grafted on to sprue. Malaria, especially the benign tertian, is a case in point, or more important still, it may be, syphilis. Experience shows that, not only do sprue patients who are the subject of an old syphilitic infection tolerate antisyphilitic treatment, such as potassium iodide and salvarsan, very well, but that the sprue itself does not improve until this has been undertaken. Sprue may be complicated by active amœbic dysentery, and in such cases vigorous treatment with emetine and emetine-bismuth-iodide may be necessary before any improvement in the sprue condition is noted. Acute appendicitis quite commonly complicates sprue. Not only do the patients tolerate appendicectomy extremely well, but the removal of the acutely inflamed appendix sometimes appears to cure the sprue. The Editor has observed several instances where the patient survived acute pneumonia and, after recovery from the acute infection, subsequently remained free from sprue-like symptoms.

Oral sepsis.—Bad teeth and pyorrhœa must be attended to after the subsidence of acute symptoms of sprue. Great care should be exercised; it is a great mistake to advocate too rapid extraction of teeth, as it is liable to provoke serious relapse.

HILL DIARRHŒA

Definition.—A form of morning diarrhœa accompanied by flatulent dyspepsia and the passage of copious liquid, pale, frothy stools. It occurs principally in Europeans on their visiting the hills after residing for some time in the hot lowlands of tropical countries. Hill diarrhœa is a frequent precursor of the fully developed disease—sprue.

Geographical and seasonal distribution.—Crombie, who gave an excellent account of this disease, pointed out that a similar affection may show itself in the highlands of Europe and Africa, as well as in those of India. It is said to occur also in corresponding circumstances in South Africa and South America. There is no reason, therefore, to suppose that hill diarrhœa is special to India, although, owing to the large European population frequenting the hill sanatoria in that country, it has been particularly noticed there. An elevation of 6,000 feet or over, when combined with an atmosphere saturated with water vapour, is particularly favourable to its development. In India it is found to begin and end with the rains. during which, in certain years and places, it is apt to assume almost epidemic characters. Thus, during the wet season of 1880, in Simla, an epidemic of hill diarrhœa affected from 50 to 75 per cent. of the European population, three-fourths of the cases happening within a week of each other. In some years hill diarrhœa is less prevalent than in others ; but at the proper season few of the various hill sanatoria of India are without examples.

Ætiology and pathology.—It is difficult to say what may be the precise factors determining this disease. The low barometric pressure associated with great elevation above the sea-level may be a favouring circumstance. Damp seems to be indicated by the fact that the disease occurs principally during the rains. Chill after exposure to the high temperature of the plains has possibly an important share. Manifestly there is a suspension of the functions of the liver, and, considering the dyspepsia and looseness, most probably of those of the pancreas and of the other glandular structures subserving digestion. Hill diarrhœa is certainly something more than an intestinal catarrh. There are no adequate grounds for connecting it with either the water or the food supply, though at one time Duncan advanced the hypothesis that mica in the drinking-water caused irritation of the intestinal mucosa.

Symptoms.—Without very obvious cause the patient, who in other respects may be in good health, soon after arrival at a hill sanatorium becomes subject to a daily recurring diarrhœa, the looseness coming on regularly every morning some time between 3 and 5 o'clock. The calls to stool are apt to be sudden and imperative. The motions passed are remarkably copious ; very watery in some instances, pasty in others. They are pale, frothy, and like recently stirred whitewash, so devoid are they of biliary colouring matter. Their passage is attended with little or no pain, often with a sense of relief. From one to half a dozen or more such stools may be voided before 11 a.m. After that hour—at all events, in ordinary cases—the diarrhœa is in abeyance for the rest of the day, and the patient may then go about his duties or pleasures without fear of inconvenience.

The distinctive features of this form of diarrhœa are, therefore, the regularity of its recurrence every morning and its cessation after a certain hour in the forenoon ; the absence of colour in the stools ; and the attendant flatulence. The abdomen is sometimes blown out like a drum, the patient being conscious of unpleasant borborygmi associated with a feeling as if

some boiling or chemical operation were proceeding in his inside. Occasionally cases are met with in which the stools are very pale although there is no diarrhœa. In a certain proportion of cases, symptoms persist and develop the clinical picture of sprue.

Treatment.—The treatment recommended by Crombie, and endorsed by other medical men of experience in India, consists of a strict milk diet, rest, warm clothing, a teaspoonful of liquor hydrargyri perchloridi in water about fifteen minutes after food, and 12 gr. of pepsin, or a corresponding quantity of lactopeptin or ingluvin, two hours later. If, in spite of treatment, the disease persists, the patient must return to the low country.

CHAPTER XXX

SPECIAL AFFECTIONS OF THE LIVER

The occurrence of a peculiar type of liver cirrhosis in Indian children was first described by Sen (1887). The disease appears to be peculiar to India, though a few cases of a similar nature have been reported from Mexico and North China. Cirrhosis of the liver of unknown ætiology is widespread in young adults in the tropics, especially in the East Indies, and this subject requires further investigation (p. 43).

INFANTILE BILIARY CIRRHOSIS

This disease is found to be more prevalent in Hindu than in Mohammedan children. Thus, in Calcutta, from 1891 to 1893 inclusive, infantile biliary cirrhosis—the name given to the disease—caused 1,748 deaths. Although the Hindu and Mohammedan populations of that city are about equal, as many as 1,616 of the deaths occurred in Hindus, whilst only 80 occurred among Mohammedans, the balance of the mortality being among the Eurasians and other races. The disease occurs principally in children under one year, rarely attacking those over three years. As a rule, it begins during dentition, or about the seventh or eighth month, running a fatal course in from three to eight months. In rare cases it may commence within a few days of birth. Instead of lasting several months, its progress may be much more rapid, and terminate in death in from two to three weeks. In India it is common in Bengal, Madras, Bombay Presidency, and the United Provinces; it is more prevalent in rural districts than in towns.

Ætiology.—The cause of infantile biliary cirrhosis is unknown. Neither alcohol, syphilis, nor malaria has anything to do with it. The children of the well-to-do are relatively more frequently attacked than those of the poor. It has also been observed that it tends to run in families, child after child of the same parents succumbing within a year or two of birth. Mukerji remarks that the disease is especially apt to occur in grossly overfed and pampered children in Bengal, and has adduced evidence that the virus is probably conveyed by the mother's milk to the child. Green-Armytage believes the true ætiology to be in a deficiency of vitamins in the mother's diet, thus depressing the mammary secretion and the endocrine system of the fœtus, overfeeding of the child when born, and the insufficient feeding of milch animals. Megaw, in India, has pointed out recently the close association between cirrhosis of the liver and bacillary dysentery. He believes the one to be the direct sequel of the other.

Pathology.—Gibbons has given an elaborate and most careful account of the pathological anatomy of this disease; he concludes that it is a peculiar form of biliary cirrhosis, the consequence of the action on the liver-cells of some irritant of gastric origin, which leads to degeneration of the cells

in the first instance, with subsequent increase of intercellular connective tissue and, later, of the portal sheaths. The formation of new bile-ducts between the hepatic cells, which is a well-marked feature, he regards as evidence of a natural curative effort having for its object a regeneration of the liver-cells. Green-Armytage calls the disease intercellular hepatic cirrhosis. R. Rao (1935) has contributed the most profound study up to date by the application of the silver impregnation method. He concludes that the disease is a subacute *toxic* cirrhosis. He emphasizes the varying degrees of necrosis of the liver cells, the avascular œdematous connective-tissue network, and the obliterative lesions of the terminal and some of the bigger divisions of the hepatic venous tree without appreciable changes in the portal and biliary trees. There is also a poor attempt at regeneration of the hepatic parenchyma.

Symptoms.—Commencing insidiously, the characteristic initial enlargement of the liver may have made considerable progress before the disease is suspected. Nausea, occasional vomiting, sallowness, feverishness, constipation, anorexia, irritability of temper, thirst, and languor call attention to the child's condition. On examination, the liver is found to be enormously enlarged, extending perhaps to the umbilicus or even lower. The surface of the organ is smooth ; the edge, at first rounded and prominent, as it begins to contract becomes sharp and distinct and can be readily grasped between the fingers, the swollen organ feeling hard and resistant. The spleen may be enlarged, as in most hepatic cirrhoses. Fever of a low type sets in ; the sallowness deepens into profound jaundice ; the stools are clay-coloured, the urine is dark with bile, and there may be a terminal ascites, with puffiness of the feet and hands. The skin may be bronzed almost as deeply as in Addison's disease. Sooner or later, death from cholæmia ensues.

Treatment.—According to Green-Armytage, when cases are seen early and parents are given the necessary instruction, recovery takes place in six to ten weeks. Whenever possible, the latest baby, in a family in which several cases of this disease have already occurred, should be immediately removed from the mother and artificially nursed.

Prophylaxis.—The mother must be fed properly in the antenatal and nursing periods. When weaning occurs, the child should be fed on good cow's milk. The child should not be fed on patent foods or sweets, and 2–3 oz. of fresh fruit should be given daily ; iodized salt (iodosol) should be added to all food, as vegetables in Bengal are deficient in salts.

Section IV.—INFECTIVE GRANULOMATOUS DISEASES

CHAPTER XXXI

LEPROSY

Definition.—A chronic infective granulomatous disease produced by a specific bacterium, and characterized by lesions of the skin, nerves, and viscera, eventuating in local anæsthesia, ulceration, and a great variety of trophic lesions. After a long course it is almost invariably fatal.

History.—Known from ancient Chinese, Indian, and Egyptian writings, leprosy was possibly introduced into Greece and Rome between 400 and 345 B.C. by the returning legions of Pompey. In the time of Celsus—53 B.C. to A.D. 7—it was still a rare disease in Italy. By the end of the seventh century it was well known in Southern Europe, and was first introduced into England about 950.

During the Middle Ages leprosy was common in Europe, so that the rulers and clergy instituted leper asylums and enacted laws for the isolation of lepers. The last British leper died in Shetland in 1798.

Leprosy still lingers in Italy, France, Portugal, Spain, Germany, and Russia, as well as in Greece, Iceland, and Norway. Our modern knowledge of the disease dates from the discovery of the *Bacillus lepræ* (*Mycobacterium lepræ*) by Hansen in 1874.

Geographical distribution.—At the present time leprosy is a disease of tropical and subtropical countries. Experience shows that the endemic area enlarges as our knowledge of the natives of uncivilized regions becomes more intimate.

In India leprosy is prevalent; in 1891 it was estimated that there were 105,000 lepers in a population of 210,000,000—a ratio of about 5 in 10,000. Recent statistics show that the highest endemic rate is in Central Africa, where, in the Belgian Congo, something like 10 per cent. of the population are lepers.

Recent introduction.—The modern introduction of leprosy into virgin soil, so to speak, has taken place in the Sandwich Islands, in New Caledonia, and elsewhere. The most recent has been into the Island of Nauru in the Pacific, where till 1920 it was unknown. It has spread there with great rapidity.

Epidemiology and endemiology. *Age.*—Cases are on record of the occurrence of leprosy as early as the first and second years of life, but are quite exceptional. Leprosy is extremely rare before the fifth or sixth year, but Rodriguez has shown that 44 per cent. of children who have lived seven to ten years with their leper parents, become infected. In the great majority of instances the disease begins between the tenth and thirtieth year. It rarely commences after 40, although it has been known to begin up to and even after 70.

Sex; occupation; social and hygienic conditions.—Apart from social conditions, as affording opportunity for contagion, sex seems to have little bearing on the liability to leprosy.

Sir Jonathan Hutchinson very sagaciously and truly remarked that leprosy is more especially a disease of semi-civilization. Savages without clothes contract leprosy rarely; the highly civilized are exempt; but when the savage begins to wear clothes and live in houses he becomes more subject to the disease than before.

Climate.—Climate can in no way be considered a cause of leprosy, which exists in all climates and in all latitudes; but it does seem to have some influence in determining, to a certain extent, the type the disease assumes. It would appear that the nodular form is more common in cold damp climates; the nerve form, in warm or dry climates. Rogers has shown that in hot, humid climates—the Belgian Congo,[1] the Cameroons, and the French Ivory Coast, for example—the morbidity of leprosy is high; in very dry tropical areas, such as Peru and South-West Africa, it is low. The conditions favouring the spread of leprosy are: high relative humidity, close and continued contact, and type of disease—the nodular being the more infective.

Ætiology.—It is now generally conceded that *B. lepræ* is the cause of leprosy, just as *B. tuberculosis* is the cause of tubercle. Authorities differ, however, as to the way in which the bacillus is acquired.

Conveyance of the lepra bacillus from man to man.—Many attempts have been made to communicate leprosy to man by inoculation; hitherto, with one questionable exception, all have failed; this was in a Sandwich Islander, who within a month suffered from leprous neuritis. He died six years later. The experiment was vitiated by the fact that members of his family were lepers.

How acquired.—There are two principal views as to the way in which the bacillus is acquired—heredity and contagion.

Heredity.—From the fact that it tends to run in families and that in certain instances it assumes the appearance of atavism, leprosy was formerly believed to be hereditary. If this were so, how explain the striking fact, brought out by Hansen, that of the numerous offspring of 160 Norwegian lepers who emigrated to America not one has become a leper? Although acid-fast

[1] Chesterman points out that the mortality from leprosy in the Congo is no higher than elsewhere.

bacilli have been found in the placenta and in the umbilical cord, the evidence of the Culion settlement in the Philippines is that leprosy is not hereditary.

Contagion.—The best authorities now believe that leprosy is propagated by contagion, and only by contagion. The same unanimity of opinion does not obtain as to the particular way in which, or medium by which, the contagium is applied; but that it passes, directly or indirectly, from the infecting leper to the recipient, nearly all are agreed to regard as being practically proved. Not only may a native of a non-leper country acquire the disease on visiting a leper country, but he may also communicate the disease to others, his countrymen, on his return to his own country. There is at least one well-authenticated example of this on record. Dr. Hawtrey Benson, in 1872, showed at the Medical Society of Dublin a leper, an Irishman, who had acquired his disease in the West Indies, and conveyed it to his brother. The Editor has seen a similar case in a woman in London, whose husband died of leprosy, and in whom the disease developed after a latent period of seven years. Nodular leprosy is potentially much more infective than is the anæsthetic form.

Probably intimate personal contact, and certain concurrence in the phases of the disease with special conditions in the health or physiological state of the recipient, are necessary for the successful communication and acquisition of leprosy. The simple implantation of the bacillus does not suffice; for, as already pointed out, of the many inoculations that have been made, only one has any claim to be regarded as having been successful.

Bacillus lepræ.—The lesions of leprosy are the result, direct or indirect, of the proliferation of the *B. lepræ* in the tissues. By some authorities it is known as the *Mycobacterium lepræ*. This bacillus (Fig. 69), in size, shape, and staining reactions, closely resembles that of tubercle. In length it is from half to two-thirds, and in breadth about one-sixteenth, the diameter of a blood-corpuscle. The ends of the rod—which is always straight—are in many specimens somewhat attenuated. By some authorities it is said to possess a gelatinous capsule. In common with *B. tuberculosis* and *B. smegmæ*, it retains carbolfuchsin stains after being treated with mineral acids, though it may be distinguished by its staining more readily with cold weak solution of carbolfuchsin, and by being decolorized more easily by alcohol than by weak acids; by the impossibility hitherto experienced of growing it on the usual culture media and of successfully inoculating it into man and the lower animals; by its tendency to occur in dense clusters and in greater numbers; and by its very generally being found inside cells or in zooglœa masses in the lymphatic spaces.

Specimens of the bacillus can be procured readily by excising a portion of a leproma; or they may be obtained by clamping a succulent leproma, pricking the now pallid tumour, and then collecting on a cover-glass the droplet of "leper juice," which, when spread out on the cover-glass, is fixed, stained, and decolorized as for the demonstration of tubercle bacilli. Better preparations are obtained by making with a small scalpel a minute incision into the compressed leproma, scraping some of the tissues from the under-surface of the skin, and smearing this with the juice on to the cover-glass.

The bacillus is found in all primary leprous deposits ; in the skin leproma—where it occurs in prodigious numbers ; in the meagre infiltration of the macular eruptions—where it is much more sparsely distributed ; in the early stage of leprous neuritis—where, also, it is present only in small numbers ; in the specific lesions of the liver, spleen, testes, lymphatic glands, and lungs. In the blood-vessels it has been found in the endothelium and, occasionally, free in the blood or enclosed in leucocytes, and by special technique with thick-drop blood preparations, this method may be used in diagnosis. After

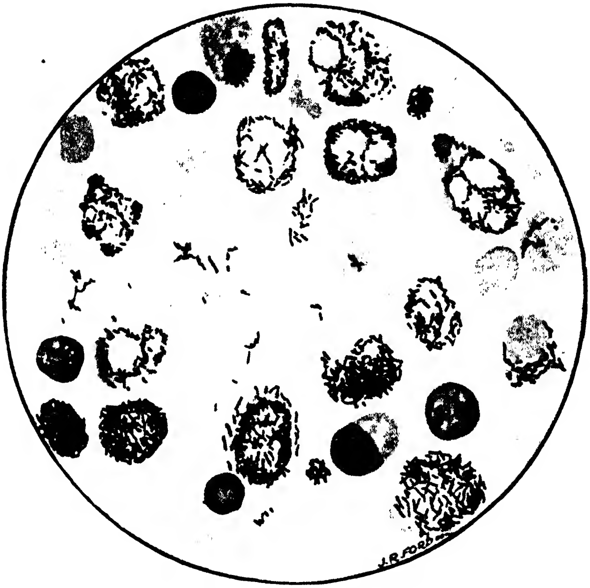


Fig. 69. - Section of spleen showing lepra cells and lepra bacilli. × 800. (*Orig.*)

dehæmoglobinization the films are stained (Ziehl-Neelsen). The Editor has confirmed the value of this method, which has been used by de Langen, Sardito, Satanala, and others. The bacillus is abundant in the purulent discharges from the nose, from ulcerating lepromata, or other forms of primary leprous infiltration. It has very rarely been found in the spinal cord or in the lungs. In nodular leprosy bacilli have been demonstrated in numbers in what appears to be apparently normal skin. One modern view is that *B. lepræ* is a streptothrix like the actinomyces, or, according to some, that like the tubercle bacillus it is pleomorphic to a high degree, and that at a certain stage of growth and under certain conditions the mycelia break up into short rods, many of which are now acid-fast.

B. lepræ has not so far been grown with certainty on artificial culture media. In 1901 Kedrowski cultured a non-acid-fast diphtheroid bacillus showing true branching. He thought that the bacillus belonged to the actinomycosis group. In 1909 Clegg cultured a weakly acid-fast chromogenic bacillus. Similar results were obtained by Duval (1910) and Twort (1910) from nasal discharge of a leper. Lleras Acosta (1938) claims successful culture on Petragnani's medium of an acid-fast bacillus isolated from the blood of nodular leprosy cases. It is said that the serum of lepers gives a positive reaction with an antigen prepared from this bacillus.

In 1912 Bayon isolated a non-acid-fast diphtheroid bacillus from a case of nodular leprosy in London.

Organisms fall into three groups:

(1) Diphtheroid bacilli.
(2) Chromogenic acid-fast bacilli.
(3) Non-chromogenic acid-fast bacilli.

Differentiation from the tubercle bacillus.—*B. lepræ* can be distinguished from the tubercle bacillus by being grouped in packets often like a packet of cigars. The leprosy bacilli stain more solidly, and when granules are present they are coarser; moreover they do not stand decolorization as well as do tubercle bacilli, especially by alcohol; with 3-per-cent. HCl they are decolorized in two hours. They stain readily by Gram's method.

The conveyance of human leprosy to experimental animals.—Adler (1937) has now succeeded in communicating human leprosy to the Syrian hamster (*Cricetus auratus*) in young splenectomized animals. A fragment of a human lepra nodule was inserted under the skin, and when the animal was killed, leprosy bacilli were demonstrated in the liver. In other animals, they were demonstrated in neighbouring enlarged and caseating glands.

"*Rat leprosy.*"—The discovery that rats (5 per cent. in Paris) are subject to a disease clinically resembling human leprosy was at first thought to shed some light on human leprosy, seeing that the lesions of rat leprosy, as it is called, are intimately associated with an acid-fast bacillus resembling that of human leprosy, and that the disease is communicable to other rats by association.

There is, however, no evidence to show that the organisms of rat and human leprosy are identical, nor that the rodent disease is communicable to man. Rat leprosy occurs also in tropical rats and has been made an object of study by Lampe and de Moor in Batavia. In nature infection occurs from a lesion of the subcutaneous lymph-glands of the groin, jaw, and mesenteric regions, and the bacilli are commonly found in the skin at the root of the tail. House-rats are most usually affected in the tropics, especially *R. rattus concolor* and *R. norvegicus*. Infection in rats probably occurs through skin injuries and by cannibalism. Kudicke and Vollmar have attempted to grow rat-leprosy bacilli in tissue-culture, and the organisms remained infective for twenty-two days. Laidlaw has succeeded in conveying rat leprosy to the Syrian hamster (*Cricetus auratus*).

Pathology.—The young leproma presents a smooth, white, glistening section, but when older becomes browner. The specific lesion of leprosy

differs from that of tubercle inasmuch as the former is well supplied with blood-vessels, contains no true giant-cells, and never undergoes caseation. If hardened, cut, and stained, the leproma is found to consist chiefly of small round cells about the size of a leucocyte, epithelioid cells, and fusiform cells, which are arranged for the most part in groups, generally around or near blood-vessels; the majority of these cells contain bacilli—some having only a few, while others are crammed with the organisms. Isolated bacilli are also found scattered through the preparation, apparently free in the lymph-spaces.

In addition to the bacilli-bearing cells, and increasing in number with the age of the lesion, a number of brown granular bodies, larger and smaller, named "globi," are to be seen; these are thought to be cells in which the bacilli have perished and become granular. In old maculæ, as well as in very old lepromata, the bacilli may be hard to find or entirely absent. In the anæsthetic maculæ the terminal nerve-fibres are degenerated. As the fusiform thickening of the larger nerve-trunks in nerve leprosy is a secondary inflammation, bacilli may not always be found, although, at the very commencement of the nerve disease, bacilli are present both in the cells and lying free between the axis cylinders. In time the affected nerves become mere fibrous cords destitute of nerve tubules.

The anatomy and the histology of the various trophic lesions are such as are found in other examples of destructive neuritis, and are in no way peculiar to leprosy.

In nodular leprosy the liver and spleen are the seat, in many instances, of a peculiar infiltration which, in well-marked examples, may be visible to the naked eye. Fine yellowish-white dots and streaks, consisting of new growth and bacilli, are seen to occur in the acini.

Sometimes in nodular leprosy the testes atrophy and undergo fibrotic changes, bacilli and globi being found both in and around the tubules, free and in cells. In all forms of leprosy the lymphatic glands draining parts in which the leprous deposit is present are affected; they are swollen and hard, and on section the gland tissue is seen to have a yellowish tinge from an infiltration which contains numerous bacilli and globi.

Albuminoid disease of the alimentary canal, liver, and spleen, and nephritis, occur in a large proportion of the cases of nodular leprosy.

Symptoms.—Although *B. lepræ* is the cause of all leprosy, the clinical manifestations of its presence are far from being identical in every case; indeed, they are almost as varied as are those of syphilis or of tubercle. As a matter of fact, in its earlier stages leprosy is far from being always, or even generally, a striking disease. Sometimes, it is true, it is suddenly and frankly declared from the outset, and progresses rapidly; but in the vast majority of cases the early lesions are trifling and are apt to be misinterpreted or overlooked, and years elapse before serious mutilation or deformity is produced.

To facilitate description, it seems advisable to divide the evolution of leprosy into stages, premising, however, that the division proposed is in great measure an artificial one.

1. *Primary infection.*—Seeing that leprosy is caused by a specific bacillus, there must have been a time in the history of every leper when the infection entered the body, but there is no local lesion to

mark the spot. Probably it is inoculated on to some accidental breach of surface, or, at any rate, intimate contact with a leper seems to be essential.

The bacillus is found in the nasal mucus in the majority of early cases of leprosy. It is therefore considered by some that the initial lesion of the disease is a specific ulceration of the cartilaginous septum of the nose which may give rise to epistaxis.

2. *The period of incubation.*—This is generally, possibly always, long, and has to be reckoned usually in years—two or three at least, it may be ten. Extreme cases in which the period varied between fourteen and forty years have been described (Norman Walker). On the other hand, cases are on record in which the incubation period was set down at three months, or even at a few weeks.

3. *Prodromata.*—Fever of greater or less intensity and occurring more or less frequently is, almost invariably, a feature of the prodromal stage of leprosy. Febrile attacks with weakness and drowsiness may recur off and on during one or two years—and may be mistaken for malaria. Dyspeptic troubles, associated with diarrhœa in some cases, with constipation in others, are also common. Epistaxis and dryness of the nostrils have been noted. Headache; vertigo; perversions of sensations—such as localized pruritus, hyperæsthesia, "pins and needles," general aching, rheumatic-like pains in loins, back, and elsewhere—all or any of these may herald the explosion of unequivocal leprosy. Lepers, as a rule, sweat little (anidrosis), and this deficiency in the sweat-glands is limited to certain areas of the body, but the liability in some instances to *excessive sweating*, which comes on without apparent or on very slight provocation, is another curious feature of early leprosy. As pointed out by Leloir, this hyperidrosis may be general, or it may be confined to particular parts, most often the trunk, the limbs being unaffected or even being the subject of anidrosis.

4. *The primary exanthem.*—In a considerable proportion of cases, after a longer or shorter period of indifferent health, sometimes preluded by an outburst, more severe than usual, of fever and other prodromal phenomena, an eruption appears on the skin (Plate XXI).

The spots may be no larger than a millet-seed, or they may occupy surfaces many inches in diameter; they may be numerous, or there may be only two or three; in some cases they may be pigmented from the outset; or they may be mere vitiliginous patches; or all three forms of maculæ may occur in the same individual—erythematous, pigmented, and vitiliginous. In not a few lepers, what in the first instance was an erythematous patch may in time become pigmented, or it may become pale; in the latter case the loss of pigment is usually associated with a certain degree of atrophy of the cutis. In certain instances the eruption of the various forms of maculæ may be preceded by local paræsthesiæ, such as a sense of burning, tingling, pricking, and so forth.

A striking feature of this and of all leprous eruptions is the loss of the hair in the affected areas. Another striking circumstance is the fact that the most hairy part of the body, the scalp, is never or very rarely affected either with leprous eruptions or with leprous alopecia. As the face, particularly the superciliary region, is prone to all forms of leprous eruption, depilation of the eyebrows is a very usual, very early, and very characteristic phenomenon. The beard, too, is apt to be patchy, particularly in nodular leprosy.

The most frequent seats of the primary macular eruption are the face, especially the superciliary region, the nose, cheeks, and ears; the extensor surfaces of the limbs; the backs of the hands; the back, buttocks, abdomen, and chest. The palms of the hands and the soles of the feet are rarely if ever attacked. At this stage of the disease the mucous membranes are very seldom affected.

5. *The period of specific deposit.*—Sooner or later, however, another stage is entered upon, a stage characterized by the deposit or, rather, growth of a tissue possessing well-marked specific characters. This deposit occurs either in the skin, or in the continuity of the peripheral nerve-trunks, or in both. If in the first situation, nodular or, as it is sometimes called, tubercular leprosy is the result; if in the second, we have nerve or anæsthetic leprosy: if in both of these situations, then what is known as "mixed leprosy" is produced.

Nodular leprosy.—This form of leprosy often appears without a well-marked preliminary macular stage, being ushered in, after a longer or shorter prodromal stage, by a smart attack of fever and the rapid development, on the face or elsewhere, of the specific lesion.

The essential element in nodular leprosy is the leproma. The dimensions, the combinations, the situations, the growth, and the decay of this give rise to the more manifest symptoms of the earlier stages, at all events, of the disease. The leproma is formed by infiltration of the deeper layers of the derma with what at first is a small-celled, somewhat dense neoplasm. In size it ranges from the dimensions of a split pea, or of a bean, to a great plaque many inches across. In colour it differs according to its age and condition, and according to the natural hue of the skin of the leper; it varies from red to dirty pink in the earlier and congestive active stage, to dark brown or dirty yellow in the later stages. It is generally—though not always, especially at first—anæsthetic to some degree, if not absolutely so; it is devoid of hair, usually somewhat greasy-looking and, perhaps, stippled with gaping sebaceous follicles. Isolated lepromata are generally round or oval; when contiguous they may coalesce, forming patches of irregular outline.

When many lepromata run together, or are closely set, the growth causes the natural folds of the skin to be exaggerated; great disfigurement, especially of the face, may ensue. The appearance becomes repulsive and "leonine" (Fig. 70).

Nodules may appear in greater or less profusion on the limbs and body; favourite sites being the backs of the hands, the external surfaces of the arms, the wrists, the thighs, and the groins.

From time to time, and at longer or shorter intervals, fresh lepromata appear, their formation generally concurring with an outburst of fever. The normal and usual fate of the nodule is either first to soften in the centre and then to be absorbed, leaving a smooth circular patch of scar tissue; or, after softening, to ulcerate and discharge a sticky, yellowish pus.

When the septum of the nose is affected, the cartilage breaks

Fig. 70.—Nodular leprosy in an Egyptian. (*Photo, Dr. H. K. Griffin, Assiut.*)

down, the tip of the organ becomes depressed, and a stinking discharge escapes from the nostrils.

The eyes, also, are sooner or later attacked, lepromatous growth spreading from the conjunctiva on to the cornea or into the anterior chamber, or originating in the iris or ciliary body. Ultimately these organs also are destroyed. The hypersecretion of sebaceous material in the region of the nose and facial lesions of nodular leprosy served in ancient times as a test for this disease; the suspected eruption being washed with water, and if the surface was not wetted, this fact was in favour of leprosy.

Fortunately, in a large proportion of cases the leper is mercifully carried off by phthisis, pneumonia, or some intercurrent affection at an earlier period, and before his disease can be said to have run its full course.

ANÆSTHETIC LEPROSY.

Showing macular rash around elbow-joint. Note atrophic appearance of skin. *(Orig. case.)*

PLATE XXII

NERVE LEPROSY.—Just as in nodular leprosy, in nerve leprosy the prodromal and macular stages may be severe, or slight, or altogether absent. Usually, however, in nerve leprosy much more frequently than in nodular leprosy, the ulterior and more distinctive lesions are preluded by a long and well-marked macular stage, during which large areas of skin are occupied by erythematous, by pigmented, or by vitiliginous patches. The ringed form of eruption is a very usual one; a red, congested, slightly elevated and, perhaps hyperæsthetic border enclosing a larger or smaller area of pale, anæsthetic, non-sweating integument—the whole resembling somewhat one of those extensive body-ringworms so common in natives of hot, damp climates, and for which these rings are sometimes mistaken. (Plate XXII.)

A frequent and very distinctive symptom of this type of the disease, occurring often about this time, is the sudden appearance of bullæ (*pemphigus leprosus*) of various sizes—one or more or a series of them—on the hands, feet, knees, backs of thighs, or elsewhere. After a few days they rupture, exposing a reddish surface which presently crusts over, exfoliates, and finally turns into a pale, perhaps anæsthetic spot with a sharply defined pigmented border. More rarely the site of the bulla ulcerates.

A time comes when evidence of profound implication of the nervous system, in the shape of severe neuralgic pains, formication, hyperæsthesia, or anæsthesia, becomes more accentuated. The lymphatic glands enlarge, and there is often considerable fever with general distress. But, whether the skin lesions increase or retrogress, evidences of profound implication of the peripheral nervous system now distinctly show themselves; the neuralgic pains still further increase, and hyperæsthesia, anæsthesia, and various paræsthesiæ, along with trophic changes in skin, muscle, and bone, the results of nerve destruction, become the dominating elements in the case.

If at this stage the ulnar nerve where it passes round the internal condyle of the humerus be examined, generally it will be found to be the seat of a fusiform swelling, perhaps as thick as the little finger. Other nerves, such as the anterior tibial, the peroneal, more rarely the median, radial, brachial, great auricular, and cervical nerves especially where they pass over a bone and lie close under the skin, can be felt to be similarly swollen. Occasionally even the smaller nerves, where superficial, can also be detected hard and cord-like. At first these thickened nerves are tender on pressure, and the parts they supply may be the seats of hyperæsthesia and acute neuralgia. By degrees the great thickening of the nerve-trunks decreases somewhat, the hyperæsthesia and neuralgia subside, and anæsthesia, paresis, muscular atrophy, and other trophic changes take their place. Another and sometimes a very striking fact in nerve leprosy is the symmetry observed in the distribution of some of the anæsthetic areas. McIlhenny has pointed out that the temperature of anæsthetic digits is from

two to three degrees lower than normal. Abscess formation on the ulnar nerve has been noted.

Step by step with the progress of the anæsthesia, atrophy of the subjacent muscles supplied by the thickened nerves proceeds. Along with the atrophy there is a corresponding distortion and a corresponding loss of power. Thus the forearm wastes, the grasp is weakened, the thenar and hypothenar eminences and the interossei melt away, and the *main-en-griffe* or some such deformity is gradually produced (Fig. 71).

In the affected nerve areas all the muscles are not simultaneously or equally attacked, so that, especially in the face, curious distortions may ensue. Owing to muscular atrophy, the eyes, after a time, cannot be closed; the upper lid droops, the lower lid becomes everted, and the eye itself may become fixed (Fig. 72). At first, owing to exposure of the organ, there is lachrymation; but by and by the secretion

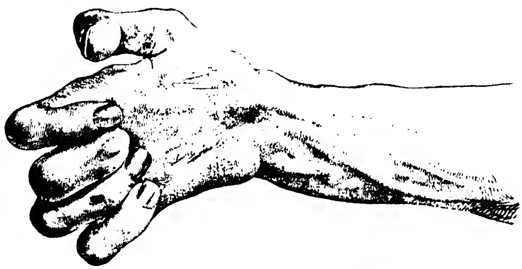


Fig. 71.—Nerve leprosy: main-en-griffe. (*After Leloir.*)

of tears dries up, the congested conjunctiva becomes cornified, the cornea ulcerates or turns leucomatous, and in the end sight is entirely lost. Ulceration often occurs in the mucous membrane of the nose, the septum being destroyed as in the nodular form; the tip of the nose may then fall down or be entirely lost. The lips, too, may become paralysed, thereby interfering with articulation and permitting saliva to dribble from the mouth in a constant stream. Changes, too, occur in the mucous membrane.

In time the skin of anæsthetic patches on the limbs tends to atrophy; it loses its glands and hairs, and, in the end, may become so thinned and tense that it actually bursts into long cracks. The nails are not generally shed, but they become rough, or thinned, or atrophied into minute, hook-like appendages.

Ulcers form over exposed parts of the hands and feet. They may penetrate and disorganize the joints, and thus often cause fingers and toes to drop off, one after another. Or, perhaps, an abscess forms around a phalanx, destroys the periosteum, and ultimately leads to loss of the bone. In any of these ways the fingers and toes are distorted or destroyed. It is no unusual thing to see on a leper's hand a finger

in which one or more of the phalanges have been thus got rid of without destruction of the fleshy part, or with only a general shrinking.

Perforating ulcer of the sole of the foot, usually under the ball of the great toe or the heel, is a very common lesion in nerve leprosy.

On the whole, the advance of this form of leprosy is much slower than that of the nodular variety.

Leprides.—Occasionally, diffuse cutaneous rashes occur on various

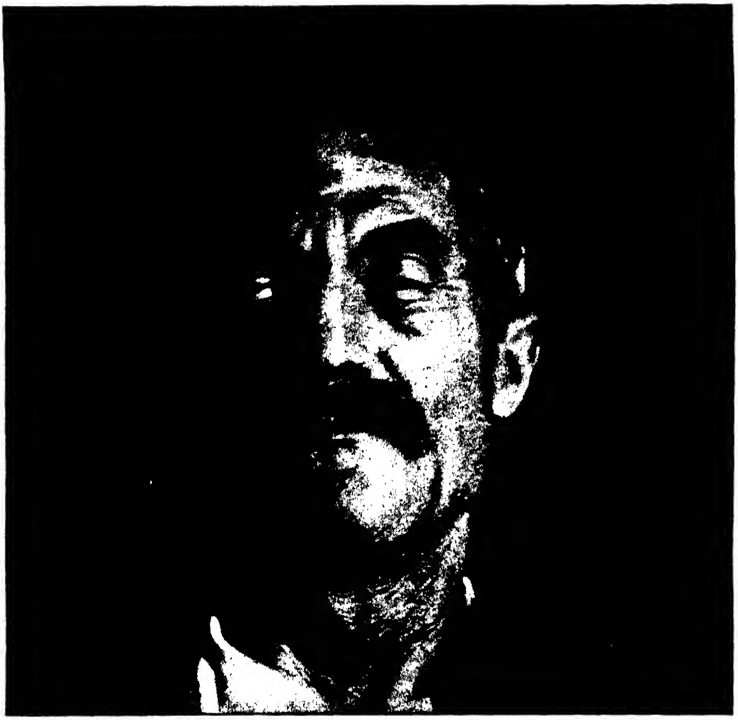


Fig. 72.—Leprotic infiltration causing paresis of facial muscles and paralysis of orbicularis palpebrarum. (*Orig.*)

parts of the body which resemble tuberculides and, like them, are regarded as an allergic manifestation of some leprotic deposit.

Diagnosis.—The touchstone in all doubtful cases is the presence or absence of anæsthesia in some skin lesion or in some skin area. Anæsthesia is rarely absent in leprosy; generally in the implicated spots it is complete, or nearly so. It should be particularly sought for towards the centre of maculæ, in the pale patches left after the fading of former maculæ, in the hands and feet, and in nodules of some standing. In no other skin disease is definite anæsthesia a symptom.

It is usually in the diagnosis of incipient cases that difficulty is liable to arise. Early deposits are frequently seen or felt on the forehead, and there is often a tell-tale thickening situated in or around the naso-labial fold. Powell has pointed out that in the majority of cases of leprosy in men hypertrophy of the nipple takes place (Fig. 73). Diagnosis of leprosy is made certain by demonstration of the bacillus.

Fig. 73.—Leprosy, showing hypertrophied nipples. (*Orig.*)

Very often, this can be done in preparations made from the nasal mucus by the discovery of acid-fast bacilli, but it must be remembered that they must maintain the correct morphology and disposition—*for all* acid-fast organisms are not necessarily *B. lepræ*. In skin lesions, it may be effected by expressing " leper-juice " and staining it by the Ziehl-Neelsen method, or by actual biopsy of the skin.

Differential diagnosis.—*Vitiligo* or *leucoderma*—sometimes called

white leprosy, and by the vulgar very generally regarded as true leprosy—bears a certain resemblance to the pale postmacular patches referred to; not to mention other features, the absence of anæsthesia in leucoderma at once settles diagnosis.

The sensory and trophic lesions of *syringomyelia* might be mistaken for nerve leprosy, but the general history of the case, the history or presence in leprosy of macular eruption, of thickened nerve-trunks, and of enlarged lymphatic glands, and the absence of these phenomena in syringomyelia, are mostly sufficient to establish a diagnosis. Generalized thickening of the peripheral nerve trunks is encountered in the somewhat rare hypertrophic peripheral polyneuritis, but which presents the picture of a general flaccid paralysis, especially of the hands.

It is possible that the early lesions of *Mycosis fungoides* might be mistaken for the early lesions of leprosy; but this is hardly possible in the fully developed picture of the disease.

The occurrence of an acid-fast bacillus in the sputum of a patient coming from a country in which leprosy is common should be regarded with suspicion, and its true nature tested by injection of the sputum into the guinea-pig, as tubercular infection commonly coexists in lepers.

It is hardly necessary to point out the diagnostic marks of leprosy as against syphilis, erythema multiforme, erythema nodosum, acrodynia (a disease allied to ergotism), trypanosomiasis, lupus vulgaris, lupus erythematosus, psoriasis, eczema, lichen planus, cheloid, body-ringworm, erythrasma, pityriasis versicolor, pellagra, and filarial elephantiasis. Mistakes can scarcely be made unless from carelessness, or by someone completely ignorant of the nature, history, and symptoms of these diseases.

Muir and Roy state that in mild early cases of leprosy positive reactions indicate coincident spirochætal disease, but in advanced cutaneous and mixed cases, on the other hand, especially those subject to attacks of lepra fever, a positive Wassermann reaction by itself does *not indicate syphilitic infection*. This reaction, therefore, cannot always be relied upon as a guide in differential diagnosis, for Lloyd, Muir, and Mitra reported that 63 per cent. of nodular cases and 27 per cent. of anæsthetic cases in adults gave positive reactions: at least three-quarters of these are due to coexisting syphilis as evidenced by the effect of antisyphilitic treatment. There remains a small residue of cases in which the positive reaction appears to be due to leprosy alone, especially in the nodular form.

When confirmation of a clinical diagnosis is required a portion of tissue may be excised for microscopic section, or the bacilli may be demonstrated in the nasal mucus or in serous fluid expressed from a nodule. By raising a blister on a nodule, or on an anæsthetic patch, by means of carbon-dioxide snow, a quantity of serum may be obtained in which on centrifugation leprosy bacilli may be demonstrated.

Rubino's reaction.—A good deal has been made recently of the value of the sedimentation-rate in the diagnosis of leprosy. Westergren's method is usually used. The citrated blood is placed in a tube up to a certain mark and the rate of the sedimentation noted in millimetres at the end of one, two, and twenty-four hours. Generally speaking, the rate is greater in women than in men. Sedimentation-rate is always decreased in leprosy, and concurrently the cholesterol content of the blood is reduced. Rubino has more recently advocated an agglutination-sedimentation test with formolized sheep's corpuscles. The sensitiveness of the reaction is clear and is never obtained in any condition except leprosy. The serum of lepers contains a specific substance which causes rapid agglutination and sedimentation of formolized sheep's corpuscles. The reaction is positive if the sedimentation is produced in less than an hour with the formolized corpuscles.

An *intradermal lepromin* reaction (an extract of lepromatous material) has been used in diagnosis, and, when positive, may be regarded as a sign of existing immunity.

Prognosis.—Complete recovery is an event so rare in leprosy that, though it may be hoped for, it must not be expected. Recovery from the actual disease itself—that is, in the sense that fresh leprous infiltration may cease to occur, and old infiltration may be absorbed, and that the bacilli may die out—is perhaps the rule in nerve leprosy; but the effects of the leprous process are generally permanent, the trophic lesions resulting from nerve destruction being irremediable. Such cases may live, however, for many years—thirty or forty—and die of some other disease, though in an appreciable proportion, according to Muir, the disease becomes arrested.

Nodular leprosy is usually a much more acute disease than nerve leprosy, sapping the strength and general health much more effectually and more quickly. It rarely runs its full course, death being brought about by some intercurrent disease, such as, and especially, phthisis, or nephritis, albuminoid degeneration of the alimentary tract, dysentery, stenosis of the larynx, or pneumonia. It may even prove fatal as a sort of "galloping" leprosy within a year of its first declaring itself.

Treatment

One is very apt to be deceived in estimating the value of a drug in leprosy. The leper applies for treatment generally during, or soon after, one of the periodical exacerbations of the disease, and when the nodules and other eruptions are active and well pronounced. In the natural course of events, and without treatment of any description, especially if the patient be placed under favourable hygienic conditions, these acute manifestations tend to become quiescent, and the disease temporarily to ameliorate; this temporary improvement is then apt to be ascribed to the drug.

Chaulmoogra treatment.—*Chaulmoogra oil* (*Oleum gynocardium*, obtained from the seeds of *Taraktogenos kurzii* in Burma and Assam;

Hydnocarpus wightiana in Southern India; and *H. anthelmintica* in Siam and China), in doses of from 2 to 10 up to 40 drops or more, according to tolerance, three times a day, together with inunction of the same drug mixed with some oil, is a favourite remedy with practitioners. Such lepers as can assimilate large doses of this drug appear to derive benefit. The oil of *Hydnocarpus wightiana* is much preferred by many observers, notably Rogers, to the former. It has the further advantage of being more easily procurable, being grown in gardens and accessible places all over the south of India, so that the seeds can be obtained fresh.

Ethyl esters of chaulmoogra.—Originally Messrs. Bayer & Co. produced an ethyl ester of chaulmoogra which they named *Antileprol;* this is put up in capsules of 15 gr. (1 grm.) each and given intramuscularly or by the mouth twice weekly, and in gradually increasing doses. Later, Dean and McDonald, in Honolulu, believing chaulmoogra oil to be inabsorbable when injected as such into the tissues, produced a similar preparation for intramuscular injection.

The ethyl esters of chaulmoogra are given as an intramuscular injection, commencing with 1 c.c. a week and gradually increasing the amount till 5 or 6 c.c. are reached. The preparation is now available as *Moogrol* (Burroughs Wellcome). The iodized ethyl esters of chaulmoogra (iodized Moogrol), are given by the intradermal method, 1 c.c. being given at weekly intervals, gradually increasing the dose till 5 c.c. are reached. The leprotic lesion should be completely infiltrated by producing coalescing "injection weals." When the lesions are so small that 5 c.c. cannot be injected into them, the balance should be given intramuscularly. At the same time calcium-iodo-ricinoleate—known as *iodicin* (B.W. & Co.)—is given in tabloid capsules by the mouth three times daily. The initial dose should be 0·25 grm. per 100 lb. of patient's body-weight, and it is recommended that it should be gradually increased till a maximum of 1 grm. per 100 lb. of body-weight is reached.

A more recent preparation is *Alepol* (Burroughs Wellcome), the sodium salts of a selected fraction of the less irritating lower melting-point fatty acid of hydnocarpus oil. A 3-per-cent. solution can usually be given subcutaneously, or intramuscularly, without causing pain, and 1-per-cent. solution intravenously. Alepol is much cheaper than the ethyl esters, and two doses given weekly for one year cost two shillings. If an equal quantity of blood abstracted from the vein is mixed with the alepol before intravenous injection, this method obviates thrombosis.

As very small intravenous doses of alepol may occasionally produce long and severe reactions, it is desirable to begin with intramuscular and subcutaneous doses of 1 c.c. of the 3-per-cent. solution (increased by 0·5 c.c. to 5 c.c. or more) twice weekly, until saturation has been obtained. In cases which do not respond well to this treatment intravenous injections may be given once a week, alternating with

intramuscular ones, commencing with 1 c.c. of a 1-per-cent. solution and increasing by the same amount at each injection to 5 c.c. or more. It is better to use intramuscular injections until reactions cease before commencing the intravenous route.

Sodium hydnocarpate in a 3-per-cent. solution is given intramuscularly or subcutaneously, twice weekly in doses commencing with 0·5 c.c. and increased by the same amount at each dose up to 5·0 c.c. or more.

Some authorities have preferred *sodium morrhuate* (1 c.c.) combined with the gynocardate.

Two other modern methods of injecting chaulmoogra must be referred to. The mixture known as E.C.C.O. consists of the ethyl ester of *Hydnocarpus wightiana*, creosote, camphor, and olive oil, given hypodermically in ½-c.c. doses, intravenously in ¼-c.c. doses, the maximum being 7½ c.c. The second form, C.E.I., is a mixture of:

Chaulmoogra	50 parts.
Sulphuric ether	50 ,,
Iodine	0·1 part.

The latter preparation should be increased up to the point of tolerance. The initial doses, given intravenously—daily injections—are 0·25 c.c., increased very gradually till 1 c.c. is reached. C.E.I. produces a considerable reaction; it may be varied with injections of E.C.C.O.

Method of intradermal infiltration.—Muir (1931) has recommended intradermal infiltration of the skin with hydnocarpus esters. The ethyl esters are treated with steam and iodized to remove their irritative properties. From 10–20 sq. in. of skin may be infiltrated by as many as eighty to a hundred punctures, with a short needle, and as much as 5 c.c. of the esters injected. A skilled worker, it is said, can perform this within two minutes. The addition of 4-per-cent. creosote to the esters renders them less irritating.

Other drugs. *Ephedrine.*—An alkaloid obtained from the drug Ma Huang, in doses of 2 gr., given in hard gelatin capsules by the mouth, is recommended by Muir for the alleviation of the distressing nerve pains of leprosy.

Sulphanilamides.—The Editor has seen one case in which remarkable clinical improvement coincided with massive dosage (4 grm. daily) of M. & B. 693. This drug appears to produce a general systemic reaction and its indications in the future treatment of leprosy should be explored.

Antimony and its salts have recently received a trial. It may be given in the colloidal form as an intramuscular injection, known as Oscol stibium, 1 c.c. being given at intervals of three days; or intravenously in the form of stibacetin, 0·2 grm. twice weekly. According to Muir, intravenous antimony-tartrate, given intravenously by the same method as in kala-azar, has the effect of controlling prolonged febrile reactions.

Carbon-dioxide snow.—Some reference must be made to what is known as Paldrock's method of treatment in Dorpat. This is the application of CO_2 snow, not only to the leprous tissue but a great

many of the nodules in the vicinity; this general effect only lasts a short time.

It is most important that coexisting syphilis should be recognized and energetically treated with salvarsan and potassium iodide. Almost equally important is it that other infections, such an ancylostomiasis and malaria, should also be cleared up. In such cases rapid improvement in the general condition of the patient ensues, as well as in his leprosy.

Intranasal therapy.—In view of the danger of contagion from the nasal discharge of lepers, this method is important. It consists of ionization of the infected nasal mucosa with 1-per-cent. sodium salts of *H. wightiana* with alepol or potassium iodide. It is said that the number of leprosy bacilli in the nasal discharge is reduced in 10 to 14 days. A current of 20–30 ma. for 20 to 30 minutes is applied to each nostril separately, and three or more sessions at bi-weekly intervals are required to clear up the local infection. Although unpleasant, the treatment is well borne, even by children.

Protein-shock therapy.—The favourable results produced by febrile reactions in leprosy have led various observers to try intravenous and subcutaneous injections of various organisms. Row, in Bombay, has recorded improvement after weekly subcutaneous injection of autolysed cultures of tubercle bacilli, washed free of fatty substance by petrol ether. Hasson has claimed remarkable results in nodular leprosy from intravenous injections of dead leprosy bacilli obtained from leprotic lesions and killed cultures of *Bacillus pyocyaneus*. A great febrile reaction is thereby produced; in order to obtain improvement, ten or more of these injections are necessary. The Editor has seen equally good results follow the intravenous injection of milk, or mixed typhoid and paratyphoid vaccine in graduated doses, and he believes that distinct benefit accrues from what is, in effect, "protein-shock" treatment in healing up intractable ulcerations. The treatment is commenced with 50 million typhoid-paratyphoid organisms, and the dose is gradually increased to 200–300 in order to obtain satisfactory reactions.

Surgical measures.—When leprous nodules spread on to the cornea and threaten to interfere with the line of vision, Brockmann has shown that the extension of the leproma may be arrested by division of the cornea on the pupillary side of the lesion; it is found that the bacilli do not traverse the cicatrix. Tarsorrhaphy for ectropion of the lower lid, iridectomy for iritis or synechiæ, tracheotomy for laryngeal stenosis, and necrotomy for bone disease, may sometimes have to be performed. Horder strongly recommends amputation for perforating or other forms of leg ulceration, as the general health is much improved by the removal of such sources of sepsis. The existence of leprosy does not materially interfere with the success of surgical operations. Manson once removed an enormous elephantiasis of the scrotum from a confirmed leper; the presence of the leprosy did not prevent sound healing of the extensive operation wound, the man making a good recovery from the operation.

Deformities may be corrected and functions restored by massage, baths and active exercise. Those with marked contractures, in which motion is absent, can be treated by deep therapy light, massage, passive extension, splinting and bandaging. Necrosis can be treated by ultra-violet rays; rarefying osteitis by the same means, massage, and exercise. Patients with nerve lesions can be treated by diathermy.

If only one tubercle or one limited lepromacule, is present, and there have been no constitutional signs of a general invasion, it is advisable to excise freely the affected spot.

Other symptoms have to be treated as they arise; laryngeal affections may require insufflation of cocaine. Leprotic iritis may be extremely difficult to treat, and often atropine drops are of little avail. In these cases hyoscine (scopolamine) hydrobromide, ½-per-cent. solution, may be used in the form of drops; it usually gives relief. For the offensive nasal discharge the following nasal lotion will be found useful:

℞	Sod. chlorid	gr.xxii (1·42 grm.)
	Sod. bicarb.	gr.xxii (1·42 grm.)
	Pot. chlorid.	ʒ ii (7·78 grm.)
	Calc. phosph.	℥ ss (15·55 grm.)

Half oz. to be used with ½-pint of warm water as a nasal douche.

The treatment of large leprotic ulcers is often a matter of considerable difficulty, because at the base there is usually some bone necrosis. Bousefield recommends the application of mild antiseptic solution and dressing. The ulcer should then be scraped, and the necrotic bone removed. General treatment should consist of intramuscular and intradermal injections of iodized chaulmoogra esters. For local antiseptic treatment 0·5–2 per cent. of copper-sulphate solutions have proved best for frequent washings and applications.

Prophylaxis.—The leper must be regarded as a source of danger and, *qua* leprosy, the only source of danger to any community he may live amongst. Therefore a sure and the most effectual way of suppressing the disease is the thorough isolation of existing lepers. There are many difficulties, however, especially in such countries as India, in giving practical expression to what appears to be a perfectly logical conclusion—difficulties springing from the rights of the individual, finance difficulties, difficulties arising from concealment or incorrect diagnosis as well as from the continued introduction of fresh cases from without.

As an instance of the possibilities open to segregation, if carried out on thoroughly practical scientific and humanitarian lines, the Culion Island Leper Colony, in the Philippines, organized and developed under Victor Heiser, may be cited. On the island is situated a town, with laundry, theatre, and schools complete. When segregation of lepers was enacted, it was found that little compulsion was necessary, owing to the obvious advantages offered to the sufferers. Some 8,000 lepers were segregated, and at the end of ten years the number had been reduced to 3,000 by natural processes and the nearly complete cessation of new infections. Such a rapid reduction within one decade

cannot be explained on any other grounds than the success of the measures adopted in removing the sources of infection. Lull reports that since special attention has been devoted to improvements in the dietary, and intensive treatment with the ethyl esters of chaulmoogra, good results have been obtained, especially with children, among whom, out of 70 cases, 54 per cent. have become negative. Since institution of these measures, 2,448 lepers have been released, and since 1907 over £4,000,000 have been spent by the Government on the segregation of lepers.

Lepers ought not to be allowed to beg in the streets—as is often the case in Eastern cities—to keep shops, or handle food or clothes intended for sale, to wander about the country as pedlars or mendicants, to hire themselves out as servants or prostitutes, or to frequent fairs and public places. A child born of a leper should at once be removed from the diseased parent and, if necessary, cared for at the public expense.

CHAPTER XXXII

YAWS (FRAMBŒSIA)

Synonyms.—Pian; Frambœsia; Boubas (Brazil); Coko (Fiji); Parangi[1] (Ceylon); Dube (Gold Coast); Purru (Malaya).

Definition.—Yaws is a contagious inoculable disease, characterized by a primary sore, and an indefinite incubation period, followed usually by fever, by rheumatic-like pains, and by the appearance of papules which generally develop into a fungating, encrusted, granulomatous eruption. Running a chronic course, it is protective against a second attack. The disease is caused by *Spirochæta* (*Treponema*) *pertenue*, and is controlled by salvarsan and certain bismuth salts. All authorities emphasize that yaws is a very widespread and disabling disease.

In this account it is impossible to delve minutely into the question of the identity, or otherwise, of yaws with syphilis. The former is now thought to be merely a primitive and tropical form of the latter. Throughout this account the reader should realize that the organisms of yaws and syphilis are indistinguishable and the lesions produced are extremely difficult to differentiate.

History.—The first descriptions, by Oviedo, of what we know as yaws did not appear until the sixteenth century. Before this period the allusions in the literature appear to be mere surmises. The deductions made from historical records suggest that yaws is of more ancient lineage than syphilis. It is clear that what we now know as syphilis appeared with dramatic suddenness at the end of the fifteenth century, and, as a new disease of devastating character, spread rapidly over Europe. According to historical records, the disease broke out after the return of Columbus to Spain. Oviedo (1478–1557) was in Barcelona at the time, and in his *Historia General y Natural de las Indias*, he stated that the disease was contracted from Indian women by the Spaniards who accompanied Columbus, that it was brought by them to Spain, and transmitted to the army of Charles VIII. Las Casas (1474–1556) in his *Historia de las Indias*, refers to a disease which was very dangerous to Spaniards, and was known as syphilis, being known in Italy as the "French malady." Dias de Isla, a physician practising in Barcelona in 1493, gives a very complete account of the disease and states that it was unknown before that year, and that it was brought by the crew of Columbus on their return from the *first voyage* to Haiti. Dias himself treated several sailors from the squadron, including the pilot, Pinçon of Palos

[1] This word means "foreigner," a term applied by the natives to the European invaders of Ceylon.

In the autumn of 1493, Charles VIII of France invaded Italy with a rabble army. He captured Naples on February 22, 1495, but a new plague (syphilis), accompanied by severe skin lesions, broke out and necessitated the evacuation of the city. The spread of syphilis can be traced, according to Pusey (1933) with the dispersal of Charles's army throughout Europe. In 1497 it reached England and Scotland. In Japan it was not recognized till 1509 at Nagasaki, where it was attributed to Chinese and Portuguese sailors.

The evidence available from bone remains tends to confirm the present view. According to the far-reaching researches of such authorities as Virchow (1896) and Elliot Smith (1930), no syphilitic bone of pre-Columbian origin has been discovered. On the other hand, Means (1925) and Williams (1932) have found the long bones of Indians showing evidences of syphilis in primitive races in North and South America; and the former found evidences of it in skeletons of the prehistoric mound-building Indians of Ohio.

Recent views on the syphilis-yaws question.—In Jamaica, Turner, Saunders, and Johnson record that no cardiac disease has been encountered in yaws cases, and this has been confirmed by radiographic examinations. In their critical survey of the disease as it appears in that island, they bring forward several new points. The "attack rate" in adults is found to be as great as in children, and yet nothing like congenital syphilis has been seen in Jamaican babies, and this is held as strong evidence against the identity of syphilis and yaws. Infants and children in Jamaica are more liable to infection than are adults, and 90 per cent. of cases contract the disease before they are fifteen years of age. All the female cases give a definite history of having contracted the disease from their yaws-infected children.

It may well be that yaws and syphilis have sprung from a common ancestor. In the case of the former it is probable that the spirochæte, under the more primitive conditions of the tropics, has been spread from man to man by intimate contact, whilst the syphilitic spirochæte under more civilized conditions, where such contact is not possible, came to be communicated by the venereal route and thereby assumed a more virulent character and evolved (as do certain other spirochætes) a neurotropic strain. Intermediate forms between the two classical forms of these diseases, which are so closely related as to be zoologically referable as "subspecies," undoubtedly have become evolved in time, as in the nonvenereal child syphilis of the Arab tribes of the Euphrates and Iraq, and known as "Bejel" (Hudson). This disease has been well described by Hudson in Mosul, Dulaim, and Amarah, where there is a high incidence of syphilis but very little gonorrhœa. The syphilis is spread by personal contact, is of low virulence, gives a positive Wassermann reaction and corresponds to the endemic syphilis of Asia Minor described by von Düring. The most frequent lesions are found in the mucous membranes of the mouth; but in other respects—in the special affinity for children, and in the production of hyperkeratosis and depigmentation—it resembles yaws, and circinate lesions of the soles of the feet, resembling crab-yaws, are common. The depigmentation of the palms of hands resembles that described by Lacapère in Morocco.

The Editor has been criticized for the inclusion of yaws in the ambit of tropical diseases and it has been suggested that yaws and syphilis should be included as one disease; rather it is better to adhere to the idea that yaws represents a form of primitive spirochætosis which is found only at the present day in the tropics. Admiral C. S. Butler, who is an ardent unicist, believes that there is only one disease "syphilis," and has cogently stated his

conclusions in a booklet, *Syphilis sive morbus humanus* (1936), in which he combats the generally accepted theory that syphilis was brought back from the New World and spread through Europe as a plague during the sixteenth century.

The term "syphilis" was first used in an allegorical poem of Frascatorius in 1530 and is the first known description of the disease extant.

Geographical distribution.—Yaws is common in tropical Africa, the West Indies, Ceylon, the Pacific islands, Papua, the East Indies, and the Malay States. In India and China it appears to be rare. Children in the West Indies and Fiji are especially liable to be attacked. Possibly yaws was originally introduced into America and the West Indies by negro slaves. During recent years it has become extremely prevalent in Kenya Colony, Tanganyika Territory, and Uganda, where it is spreading with great rapidity. On the other hand yaws has disappeared to a great extent from Guiana, Ceylon and Barbados, where it was previously extremely rife.

Epidemiology and endemiology. *Contagion and heredity.*—As yaws is highly contagious, all circumstances favouring contact with the subjects of the disease favour its occurrence. Simple skin-contact does not suffice; a breach of surface is necessary. The knowledge that the secretions from yaws lesions could transfer the disease to another person was well known to the slaves of the West Indies, and furthermore, they practised auto-inoculation in their children who did not show a generalized eruption.

The disease frequently commences in a pre-existing ulcer, the organism (Spirochæte) being conveyed by flies to the previously lacerated surface (p. 621). Cases are prone to originate in certain dirty houses, the virus from previous yaws patients seemingly impregnating the floors and walls of the filthy huts in which the latter have resided. In this manner the disease may be, and in some cases no doubt is, acquired without direct transference from an existing case. In some countries, as in Ceylon, yaws is a disease of the flat, low-lying districts, while practically absent from the hill country; in Assam, on the other hand, it is more common among the hill tribes than among dwellers of the plain. Ramsay has shown in Assam that native hill people who only exhibit obscure lesions, such as condylomata, while living at high altitudes, develop florid yaws when they come down to the plains. In Jamaica, Saunders and Kumm have emphasized the importance of rainfall and geological formations on the distribution of yaws. Wherever there is porous limestone there is little or no yaws.

Yaws is neither hereditary nor congenital. A pregnant mother suffering from yaws does not give birth to a child suffering from the disease, nor one which will subsequently develop yaws unless the virus be first introduced directly through a breach of surface after birth. It is not conveyed by the milk; nor does a suckling suffering from yaws necessarily infect its nurse.

This statement should be qualified by the well-known fact that a syphilis-infected mother does not inevitably transmit the disease to her offspring, and if she does transmit, she may do so irregularly, not to one child, but to the next, and to one only of twins.

Although two-thirds of the cases in the West Indies, Pacific Islands, and

Ceylon occur before puberty, no age is exempt. Three males appear to be infected to every one female. It has been frequently remarked that yaws shows a predilection for certain native races. On the whole the negro and negrito stock is specially liable to be severely attacked.

Yaws at the present day shows a striking limitation to the tropics, but it is a disease so readily communicable by direct contact that it seems remarkable that it does not spread in temperate regions. In the tropics yaws is limited to low level areas, and it is restricted to rural districts with primitive sanitation. In Haiti, for instance, yaws is the disease of distant villages and syphilis with chancre is common in the main town. In the Philippines it is the same: in the country, yaws; in Manila, syphilis.

Ætiology.—In 1905 Castellani demonstrated in scrapings of yaws tissues an extremely delicate spirochæte—*Spirochæta pertenue*—very like that of syphilis. To demonstrate this spirochæte, slides should be prepared from scrapings of an incised yaw papule before it has ruptured. The films may then be stained with Giemsa, or made by the indian-ink method; better still, the living parasites may be detected in fresh undried films by dark-ground illumination. A fully developed yaw is unsuitable because, in consequence of its having been exposed to external sources of contamination, a variety of organisms will be present and may confuse the observer. Opinions differ with regard to the exact morphology of *S. pertenue* but later observers, including Dobell, have been unable to distinguish any structural differences between this spirochæte and *S. pallida* of syphilis (Fig. 209, 5, p. 892).

S. pertenue has been found in the spleen, lymphatic glands, and bone-marrow; doubtless it occurs in the blood. It is inoculable into monkeys and rabbits; in the former, especially in the orang-outang, it gives rise to lesions similar to those met with in the human subject.

Cultivation of *S. pertenue* was successfully performed by Noguchi in ascitic fluid containing a piece of fresh animal tissue such as the kidney, the whole being covered with a layer of sterile paraffin. This rather complicated technique has been simplified by the later work of Hata, who substituted horse-serum, the inoculation being made through the upper solidified layer. To succeed in the cultivation of these spirochætes, strict anaërobiosis is necessary.

Kumm has brought forward strong evidence that in Jamaica, at any rate, a minute fly, *Hippelates pallipes*, carries the spirochæte from one person to another. He has collected the flies at the rate of 5,000 per hour from one ulcer; they crawl under the scab and ingest large numbers of *S. pertenue*, which are afterwards regurgitated. *H. pallipes* is an oscinid fly having peculiar mouth-parts, with projecting spines on the pseudotracheæ and labellæ.

Yaws can be successfully inoculated into monkeys by direct subcutaneous inoculation. Schöbl (1928) inoculated *Cynomolgus philippinensis* with emulsified material from yaws. When the inoculations were made on the eyebrows, an indurated papule appeared in three to five weeks. By super-infection, or by repeated inoculation, he was able to produce a generalized yaws in monkeys. Hoffmann has shown that the South American marmoset is also a valuable experimental animal.

Pathology.—No visceral changes have been found peculiar to yaws. An important point of contrast in the morbid anatomy of yaws and of syphilis is the absence of endarteritis in the former and its frequency in the latter.

Symptoms. *As in syphilis, the symptoms of yaws can be divided into three stages—primary, secondary, and tertiary.*

PRIMARY LESION (*madra buba* or "mother yaw").—According to Sellards the *incubation period* in experimentally-inoculated yaws in man is three and a half to four weeks; in experimental apes it may be as long as three months. Naturally-acquired yaws is reputed to have, as a rule, a longer incubation period than the inoculated disease. The primary lesion may appear as a granuloma or a papule at the site of inoculation 1–7 cm. in diameter, and is known as the "frambœsoma." It may develop at the site of some old skin lesion. It is ordinarily extragenital, and may be situated on any part of the body. It may occur on the buttock, thigh, knee, leg, arm, breast, or lip (Fig. 74), but is rare on the scalp. The lower part of the leg is the site of predilection: the breasts of nursing women and the mouths of suckling babies are not uncommon sites. In Moss and Bigelow's large series the genitalia were the seat of the primary lesion in 1 per cent. only. In native women it is frequently observed at the bend of the elbow, or on the hip, and is contracted in this situation from carrying their children who are infected with the disease. The primary lesion may be so small as to escape detection; it may be single or multiple, and, in fact, great difficulty may be experienced in differentiating it from allied cutaneous lesions, but, as a rule, it is remarkably persistent, lasting from two to four months, and it may persist for a year or more.

Fig. 74—Primary yaws sore on lips of Australian aborigine child. (*Dr. H. Basedow. Adelaide*)

According to the Jamaican Yaws Commission, the primary lesion is found on the lower extremities in over 70 per cent. of cases. In 39 cases it was found:

On head, face and neck in	1
On upper extremities ,,	4
On genitalia ,,	1
On leg ,,	12
On ankle and foot ,,	21

The lesion on becoming larger becomes covered with a yellowish secretion or scab. It is at this stage known as the "mother or master yaw," the "mama pian" of the French. In ordinary locations yaws lesions are not painful unless firmly pressed.

The appearance of the lesion is preceded by a certain amount of constitutional disturbance. The intensity of the general symptoms varies within wide limits; sometimes they are hardly perceptible and are not complained of, but usually there is well-marked malaise with rheumatic pains. Occasionally there is severe constitutional disturbance lasting for about a week, with rigor, smart fever (100° to 103° F.), persistent headache, pains—worse at night—in the long bones, joints, and loins, and sometimes gastric disturbance and diarrhœa, especially in children. The lymphatic glands in the immediate vicinity become enlarged. During the decline of these constitutional symptoms the secondary eruption appears. The Wassermann reaction becomes positive three to four weeks after the primary lesion and rapidly grows stronger in titre. In the early lesions the endothelial proliferation and perivascular round-cell infiltration, so characteristic of syphilis, is present.

Secondary stage.—This is ushered in by a fine, light-coloured furfuraceous desquamation. The skin becomes harsh and dry, loses its natural gloss, and here and there the patches of desquamation (best appreciated with the aid of a hand lens) are formed. These patches are mostly small and circular; occasionally they are oval, irregular, or form rings encircling islets of healthy skin scattered irregularly over limbs and trunk; sometimes they are almost confluent, the patches coalescing and giving rise to an appearance as if the entire skin had been dusted over with flour. On the other hand, this furfuraceous desquamation may be so slight as to be overlooked. In some instances the heaping-up of desquamating epidermic scales produces white marks, very evident on the dark skin of a negro or oriental.

This patchy, furfuraceous condition of the skin occurs, not only in the early stages of yaws, but may persist throughout the attack, or may reappear as a fresh eruption at any time in the course of the disease. This condition has been described by Schöbl and Sellards as "keratoid exanthem" in artificially-inoculated yaws.

Appearance of the yaw (Fig. 75).—When the furfuraceous patches have been in existence for a few days, minute papules appear in them. This very characteristic eruption, from which the disease takes one of its names—*frambœsia* (or *raspberry*)—breaks out three months after the primary lesion. These secondary lesions may vary in size from a pin's head to half a crown, and, according to Spittel, they commence around the primary sore ("mother and daughter yaw"). The itching produced by these sores is usually considerable. As in syphilis, the eruption may be very pleomorphic; it may be roseolar, or consist of macules with desquamation resembling a squamous syphilide. It may appear on any part of the body, especially in exposed situations and on the anterior surface. The papules occur in groups, the larger appearing to be surrounded by a group of satellites, which has given rise to the various native designations for yaws. Auto-inoculation is probably responsible for the appearance of these

lesions in symmetrical fashion whenever the skin or mucous surfaces come into intimate contact; they are present at the angles of the mouth, in the axillæ, in the anal cleft, and in the inguinal region;

Fig. 75.—Secondary yaws in a Malay boy. (*W. E. Le Gros Clarke.*)

in contradistinction to syphilis, they are rarely present on the true mucous surfaces, but often in clusters just inside the nostril. Several of the groups may coalesce to cover a large surface.

The yaw is pushed up from the rete Malpighii through the horny epidermis, which breaks over their summits and splits in radiating

lines from the centre, the necrosed segments curling away from the increasing papule. Soon a yellow point appears around a hair follicle, consisting of a cheesy-looking substance, which cannot be wiped away unless undue force is used.

The papule, having arrived at this stage, may either cease to grow, the apex becoming depressed, or may go on to the formation of the typical yaw. In the latter case the lesion gradually grows into a rounded excrescence, the yellow material at the top widening out so as to form a complete cap encrusting the little tumour. The smaller tumours are hemispherical; the larger are more flattened or even depressed at the centre, possessing everted, somewhat overhanging, rounded edges. Occasionally, though rarely, a big yaw may include an area of sound skin.

The firmly adherent crust which caps and encloses an uninjured yaw is yellowish, granular, blotched with blood-stains and encrusted dirt. Deprived of its crust, the little swelling is seen to be red in colour, generally smooth and rounded on the surface, and oozes pale yellowish serum, in which spirochætes may be demonstrated; when inspissated, this serum forms a fresh cap to the yaw, and on microscopic examination is found to be teeming with the organisms. According to size, it stands out anything from $\frac{1}{8}$ to $\frac{3}{4}$ in. above the surrounding healthy skin. Pus, unless as a consequence of irritation, is not, as a rule, found under the crust.

Although the formation of the papules and yaws is attended with much itching, the yaw itself is not at all sensitive; the tumour may be touched, with acid even, without causing pain—a diagnostic point of some importance. Sometimes, as in syphilis, the eruption has a circinate character, the so-called "ringworm yaws." The itching of yaws lesions is a point of differentiation from syphilis, but, as Blacklock has pointed out, this symptom may be connected with conditions of exposure to insect bites, dirt, etc., to which native races are liable.

The yaw usually attains its maximum development in two weeks. For several weeks longer it remains stationary before beginning to shrink. The crust then thins, shrinks, darkens, separates at the periphery, and at last falls off, disclosing at the site of the former fungating mass a slightly thickened spot of fairly sound skin, which, though pale at first, may subsequently become hyperpigmented.

Histologically, the individual yaw consists of hyperplasia of the true epidermis and formation of granulation tissue; giant cells may be present.

Sometimes the secondary rash takes on a papular appearance, when the lesions are known as "acuminate papules." These are symmetrically distributed over the back, shoulders, arms, elbows and knees, and much resemble a follicular syphilide. Secondary lesions may last from six months to a year. Simultaneously with the appearance of the eruption, as in secondary syphilis, there may

be a uniform, painless enlargement of the lymphatic glands, in the aspirated lymph of which the specific micro-organism may be demonstrated. When the lesions subside, pigmented spots remain as in secondary syphilis, and are specially noticeable on the palms of the hands.

Lichenoid eruptions.—*Lichen frambœsianus* ("*Pian datre*") is a lichenoid generalized eruption of the skin described by Dutch writers in the East Indies. It is a micropapular eruption which is very striking in appearance and is not associated with *yaws papules*. It is, of course, analogous to secondary lichenoid eruptions in syphilis, and must be distinguished from other lichenoid eruptions, such as lichen ruber planus, lichen pilaris and lichen scrofulosorum. It is now generally recognized as an early secondary manifestation in

Fig. 76.—Tertiary yaws ulceration on forearm of European. (*Orig.*)

children and young adults. It is the same condition as has been described by Nicholls as "furfuraceous desquamation" and by German writers as the early frambœsiform efflorescence. The lichenoid eruption is apt to occur in patches over the shoulders and, according to Deibel and Elsbach, there is a tendency to hyperpigmentation of the peripheral micropapules, associated with depigmentation of the centre.

The serum of patients in the secondary stage gives marked positive Wassermann and Kahn reactions, and this makes the differential diagnosis from syphilis, by these means, impossible.

Tertiary stage.—It sometimes happens that the tumours, in place of becoming absorbed, break down and ulcerate, the ulceration, however, which may last for years, being confined to the yaw itself. In other instances ulceration goes deeper and extends circumferentially, giving rise to extensive sores with subsequent cicatricial contractions. Such ulcerations occur in about 8 per cent. of cases and may, or may not, be encrusted. (Fig. 76.) With the development of the deeper and

wider forms of ulceration the typical lesions of yaws may disappear for a time, or perhaps permanently. In the latter case the ulcers are said to be non-infective. Ulceration of the greater part of the limbs, especially the leg and ankle, may take place. Tertiary manifestations are seldom observed in cases which present late secondary lesions. The serum of these cases gives positive Wassermann and Kahn reactions,

Fig. 77.—Tertiary yaws. Onychia of fingers.
(*W. E. Le Gros Clarke.*)

but the cerebro-spinal fluid, in cases of advanced ulceration of the nose and other parts of the body, gives a negative Wassermann reaction with normal cellular and biochemical contents (Fernando and de Ogampo).

Lesions of the hands.—A scaly condition of the palms of the hands may persist for years. A multiple dactylitis, with uniform swelling of the phalanges, onychia, paronychia, atrophy of the nails, and subsequent deformity, is often observed. (Fig. 77.)

Foot yaws ("Dumas," or pink parangi—Ceylon; "crabs," or "crab yaws"—West Indies).—When a yaw develops on the sole of the foot, in consequence of being bound down by the dense and thick epidermis, it causes much suffering. Spreading laterally under the

Fig. 78.—Foot yaws, or "crab yaws." (*Dr. J. G. Reed.*)

thick, leathery, and unyielding epidermis, it may attain a large size. After a time the epidermis over the growth gives way, splitting up in a radiating fashion (Fig. 78). Pressure being thus removed, the yaw fungates, and suffering diminishes. Crab yaws may last a lifetime after infection in childhood. Chesterman suggests that in the foot lesions a fixation point for *S. pertenue* is formed. A condition known

as "clavus" in Dominica results from the healing of these granulomata; the centre of the core drops out, leaving an irregular erosion of the sole of the foot, or there may be deep fissures or cracks. A similar condition of pitting occurs on the palms of the hands. According to Sayers, this is the commonest lesion of yaws in the Solomon Islands, and causes great disability, especially in children; and when bilateral it incapacitates them from walking.

Gangosa, or destructive ulcerous rhino-pharyngitis (Fig. 79), which is now generally regarded as a sequel of yaws, usually commences as an ulcer on the soft palate. Slowly spreading, it may make a clean sweep of the hard palate, the soft parts, cartilages and bones of the nose, sparing the upper lip, which is left as a bridge across a great chasm, the floor of which is formed by the intact tongue. A most offensive odour is given off from the ulcerated surface. The disease may be arrested spontaneously at any period of its progress, and long before so extensive a mutilation as that described has been effected: but it is always a longstanding and chronic affair and may linger as an indolent ulceration for years. As a rule, the larynx is spared; but although phonation may be retained, articulation is seriously impaired. Gangosa occurs at any age, but is rare in young adults, though Leyes states that in Guam he has seen it in children of 3, 4, and 9 years of age. It is very common in parts of the West Indies (Dominica, 60 cases in a population of 2,000), Guam (1·5 per cent. of the population), the Carolines, Fiji, Ceylon, British Guiana, and West, Central, and East Africa. It is often found associated with the bone lesions of yaws.

Fig. 79. Gangosa in an Australian aborigine. (*Dr. H. Basedow, Adelaide.*)

Goundou, or Anákhré ("*Gros Nez*").—In 1882 MacAlister drew attention to what were termed the horned men of Africa, and in 1887 Lamprey gave further details illustrated with drawings. The natives call the disease goundou and anákhré. Later observations that have been made show that it has a wide distribution in Central Africa and South America, and that a similar disease occurs in the larger apes, chimpanzees, and baboons. An ancient Inca skull from Peru, described by Letulle, shows the characteristic lesions of goundou.

Stannus and Hamerton have shown that in the apes the hyperostosis is probably the after-result of osteitis cystica.

Goundou usually commences during childhood, although adults also may be attacked. The earliest symptoms are severe and more or less persistent headache which, after a time, is associated with a sanguino-purulent discharge from the nostrils and the formation of symmetrical swellings the size of a small bean at the side of the nose. Apparently the swelling affects the nasal process of the superior maxilla. The cartilages are not involved. After continuing for six or eight months, the headache and discharge subside. Not so the paranasal swellings; these persist, and continue slowly and steadily to increase until in time they may attain the size of an orange, or even of an ostrich's egg. As they grow, the tumours, encroaching on the eyes, may interfere with the line of vision and finally destroy these organs. In severe cases there is a general diffuse hyperostosis of the anterior part of the maxilla. There is no pain in the tumours themselves. The superjacent skin is not involved, being healthy-looking and freely movable. The tumours are oval, with the long axes directed downwards and slightly from within outwards (Fig. 80). The nostrils are bulged inwards and more or less obstructed. The hard palate is often affected, resulting in the most hideous deformity. General glandular enlargement may be noted. Traumatism seems to predispose to the development of goundou.

Fig. 80.—Goundou.
(Dr. P. M. Shepherd.)

A case of goundou associated with tertiary syphilis has been described in London by Sharpe. The patient had never been in the tropics. The lesions resembled the paranasal swellings so characteristic of goundou.

According to recent accounts, cases of goundou in Jamaicans invariably give a positive Wassermann reaction.

The bony outgrowths, not necessarily bilateral, are attached to the nasal bone and nasal process of the maxilla, but according to Botreau-Roussel and Clapier they are not entirely confined to this region; a similar hyperostosis may coexist on the tibia, upper or lower jaw, forearm, femur, or clavicle. There is a general opinion at present that goundou is a systematized hypertrophic osteitis connected in some way with yaws.

The association of *goundou* with yaws is questioned by some. In the present edition this arrangement has been made as a matter of convenience. The bony changes of goundou consist of hyperostosis, which may on the one hand be limited to the ascending or nasal processes of the superior maxilla, or be more widespread and affect the other bones of the skull as well, with an ever-present tendency to the formation of bosses of overgrowth and to the obliteration of adjacent cavities. The underlying pathological process is an osteo-periosteal dyscrasia, and the end-result is the production of finely-porous bone.

As yaws and syphilis are so closely allied, it might be expected that similar lesions might be found in the generalized osteitis of syphilis, but there appears to be very little evidence in that direction. There is very little difference between the bony changes of goundou and those which have

Fig. 81.—Distortion of fingers in tertiary yaws. (*Orig.*)

been called *leontiasis ossea*, and according to Stannus, hyperostosis of the facial bones has been recorded in Paget's disease—*osteitis deformans*. According to modern knowledge then, it seems possible that goundou is more akin to *osteitis fibrosa*, due to interference with the bony metabolism and an endocrine disorder, and it may well be that in this instance yaws constitutes the non-specific factor acting on an ill-fed native child population. Goundou-like swellings in horses, monkeys and young pigs (" cachexie osseuse ") point to osteitis fibrosa being the initial stage of this condition and all changes between cystic disease of the bones and hypertrophic exostosis can be traced in a series of skulls.

Treatment consists in incising and displacing the periosteum and chipping away the bony outgrowth with a chisel. Early cases, according to Botreau-Roussel, yield to intravenous and intramuscular

injections of neosalvarsan, four or more injections being necessary before improvement is observed. This observer has operated with success upon 113 out of 130 cases observed on the French Ivory Coast and the reader is referred to his monograph (Masson et Cie., 1925) for further information.

Periostitis, osteitis, and epiphysitis (Figs. 81, 82, 83).—Circum-

Fig. 82.—Tibial periosteal nodes, ulcers, and deformity of phalanges in yaws. (*Orig.*)

scribed painful periosteal nodes are frequently met with on the anterior aspect of the long bones, especially the radius, ulna, and tibia. The swellings are hot and exquisitely tender, and the superjacent skin is tense and stretched. After the subsidence of the acute stage, hard, firm periosteal nodes remain. A diffuse osteitis may result in a sabre-shaped deformity of the long bones, especially the tibia, though occasionally the arms and fingers. A rarefying process is also as work, for such bones are subject to spontaneous fracture with resulting

malunion, accidents which are of common occurrence in those districts in which yaws is endemic. Hackett, who has studied the sabre-shaped tibiæ of the aborigines of Australia, believes that syphilis does not occur among these peoples, and that the bone lesions are due to yaws. Colloquially known as "boomerang leg," the deformity is an anterior-posterior curvature below the knee with a forward convexity ; occasionally there are bosses of localized periostitis. Radiographs show that areas of rarefaction appear early and the bone becomes deformed. The appearances depend upon the severity of the initial lesion and the time which has elapsed since the onset of the disease. Other lesions of yaws, including gangosa, have been noted in central and northern Australia. A chronic periostitis of the clavicle is of frequent occurrence in Fiji.

Fig. 83.—Sabre-like deformity of tibia, radius, and ulna, and multiple cutaneous ulcerations, in yaws. (*Orig.*)

These bone changes are accompanied by intense rheumatic pains, and have received distinctive names, such as "sasala" (Fijian).

Juxta-articular nodules.—Fibrotic tumours situated over the olecranon, the lower end of the femur, and in other situations on the long bones, are now regarded as a tertiary phenomenon of yaws. Formerly they were regarded as constituting a disease *sui generis*, but those cases which have been investigated invariably give a positive Wassermann reaction. Originating subcutaneously, these nodules may reach the size of a small orange (Fig. 84). They are remarkably painless, and very rarely ulcerate or suppurate. Juxta-articular nodules are generally multiple, and usually occur in the neighbourhood of the joints, but, according to Steiner, may occur scattered over the body. Similar lesions have been described in tertiary syphilis, and the *Spirochæta pallida* has been isolated from them (Hu and Frazier), while Hudson found the same condition in "bejel," the non-venereal syphilis of the Arabs, among whom it occurs in 21 per cent. of all thus afflicted and is known locally as "rik." According to Frontoynant

and Girard, they contain uric-acid crystals. In Africa they are apt to be mistaken for cysts of *Onchocerca volvulus*.

Skin lesions.—The healing of subcutaneous gummata is frequently followed by depigmentation of the skin, resulting in light-coloured or leucodermic patches, especially visible in native races. A macular depigmented exanthem limited to the hands, wrists, feet and ankles is pathognomonic of yaws and was first described by Ziemann as "melung." The contractions resulting from scar tissue may lead to partial ankylosis of joints, and in severe cases to the destruction of lymph-channels and the production of elephantiasis in the affected limb.

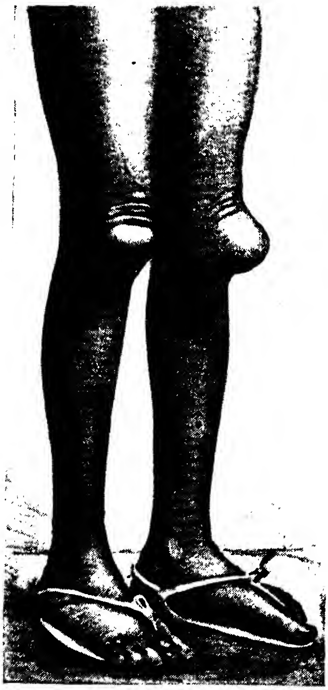


Fig. 84.—Juxta-articular nodules.
(*Photo: Dr. Watt.*)

Synovitis.—A chronic synovitis, analogous to that of tertiary syphilis, often associated with bone lesions, and, it may be, with disorganization of the joint, may be noted.

Ganglion and other lesions.—The frequency of tenosynovitis and ganglion-formation in the region of the wrist has been noted by Graham, Moore, and other observers. These ganglia are usually associated with tenosynovitis and, as extra proof of their origin, they both respond in a remarkable manner to treatment with neosalvarsan and bismuth. Stricture of the mouth due to tertiary yaws has been recorded.

The general health.—Except during the initial fever, or during one of the recurring febrile relapses, the general health is not, as a rule, affected. Occasionally, however, there are debility and cachexia; or there may be enlargement and tenderness of the lymphatic glands. In other instances rheumatic pains are a principal feature and may be very severe.

Immunity.—After the subsidence of the secondary stage a considerable degree of immunity is produced, but Sellards and Goodpasture have shown that this is relative only, for they successfully reinoculated with the disease patients who had undergone a course of salvarsan treatment. Apparently saturation of a community with yaws virus produces a relative immunity to syphilis On these grounds may be explained the apparently well-authenticated fact that syphilis is absent amongst the Polynesians of Fiji, Tonga and Samoa, in whom

yaws is especially prevalent. Formerly Fijians were in the habit of inoculating their children against yaws to protect them against subsequent attacks of the disease. As far as accurate experiments have gone, immunity to syphilis is acquired much earlier than in yaws.

Duration and recurrences.—Yaw lasts for weeks, or months, or years, its duration depending on the general health, idiosyncrasy, hygienic conditions, and the treatment employed. Mild cases in healthy subjects terminate in about six weeks; the average duration of an attack of yaws is estimated at about one year. In other instances, especially in the debilitated, the disease runs on for months, successive crops of eruption being evolved. Sometimes these recurrences may stop short at the stage of desquamation, or at the papular stage, or they may proceed to the formation of typical yaws. They are usually preceded by feverishness and pains in the bones and joints, and the successive crops may either be limited and partial in their distribution, or general.

Sequelæ.—Harper in Fiji believes that late manifestations of yaws occur as in syphilis and that they produce neurological conditions resembling those of locomotor ataxia and general paralysis, and Lambert has recorded in the South Pacific 42 cases of Melanesians and Polynesians who have died in Samoa of G.P.I.; furthermore, in their cases aneurysmal dilatation and aortic disease are comparatively common. Chossier, in routine post-mortems in Haiti, has also found aneurysms and other arterial degenerations. Recent writers, too (Blacklock), in assessing the clinical differentiation of yaws and syphilis, have remarked upon the comparative rarity of visceral and neurological lesions of the latter amongst native races. Chesterman has remarked upon the comparative frequency of new growths following yaws and has recorded melanoma implanted upon crab yaws of the foot.

Mortality.—Although in the literature of the subject reference is made to deaths from yaws, yet, judging from the statistics collected by Nicholls, the mortality must be very small indeed.

Diagnosis.—A painless, insensitive, larger or smaller, circular, encrusted, red, granulomatous excrescence occurring in an endemic district is almost certainly yaws. The most important point in connection with yaws, as regards both diagnosis and ætiology, is its relationship to *syphilis*. Both diseases may concur in the same individual (Powell cites two cases, and Charlouis two, of syphilis supervening on yaws); and antecedent syphilis certainly does not confer absolute immunity to yaws, nor antecedent yaws to syphilis. The serum in both diseases, as we have seen, gives a positive Wassermann reaction. Yaws may die out in a community, as in British Guiana (Daniels), yet syphilis remain; yaws may be universal in a community, as in the Fijians, Tongans and Samoans, and yet true syphilis, whether as an acquired or as a congenital disease, be unknown. In yaws, Hutchinson's

famous syphilitic triad—the characteristic notched teeth, nerve deafness, and interstitial keratitis—are absent.

The following table shows at a glance the main points of differentiation between this disease and syphilis.

Yaws	Syphilis
Not congenital.	Congenital.
Primary sore—extragenital.	*Primary sore*—usually genital.
Secondary stage	*Secondary stage*
(*a*) Typical yaw pathognomonic; furfuraceous desquamation and plantar lesions characteristic.	(*a*) Seldom imitates framboesia.
(*b*) Mucous membranes not affected.	(*b*) Mucous membranes affected.
(*c*) Itching common.	(*c*) Itching rare.
(*d*) Alopecia unknown.	(*d*) Alopecia may occur.
(*e*) Eyes unaffected.	(*e*) Iritis common; choroiditis and retinitis rare.
Tertiary stage	*Tertiary stage*
(*a*) Visceral lesions absent.	(*a*) Visceral lesions occur, *i.e.* pericellular cirrhosis, gumma of liver, kidney, etc.
(*b*) Nervous system not usually affected.	(*b*) Nervous system prone to infection: tabes, G.P.I.
(*c*) C.S. fluid always negative Wassermann (Fischer; Turner, Saunders and Johnson).	(*c*) C.S. fluid usually positive Wassermann.
(*d*) Blood-vessels: no endothelial proliferation as in syphilis.	(*d*) Endarteritis obliterans of viscera—cerebral thrombosis.
Yaws better resisted. Constitutional disturbance slight; great exuberance of eruption and cheloid scarring.	Syphilis attacks constitution, affecting the vital structures.
Does not respond to mercury.	Responds well to mercury.

Treatment

General measures.—All are agreed as to the propriety of endeavouring, by good food, tonics, and occasional aperients, to improve the general health. Most are agreed as to the propriety of endeavouring to procure a copious eruption by stimulating the functions of the skin; by warm demulcent drinks; by a daily warm bath with plenty of soap; and, during the outcoming of the eruption, by such diaphoretics as liquor ammoniæ acetatis, guaiacum, etc. Warm clothing is indicated. In crab yaws a local application of 2-per-cent. tartar-emetic ointment in vaseline is very useful.

I. Salvarsan, neosalvarsan (Neoarsphenamine[1]).—Except where much bone destruction has taken place, salvarsan, or better still its more recent and more soluble derivatives, has an almost magical

[1] Throughout this account the terms arsphenamine and neoarsphenamine are given as the American equivalents of salvarsan, neosalvarsan, etc.

curative effect upon yaws in every stage of the disease. The most generally used drug at the present time is neosalvarsan (neoarsphenamine). It is given intravenously to adults, and, if possible, to children ; or intramuscularly (0·4 grm. dissolved in oil, into the buttock). The more urgent symptoms yield much more rapidly than do those in syphilis, and relapses are not so common. It is curious to note that since the introduction of salvarsan the natives of the Congo are averse to receiving treatment till the secondary rash is well out. For adults the intravenous dose advocated is 0·6–0·9 grm., for young adults 0·6 grm., for children up to ten years of age 0·3 grm., and for children under two years, 0·1 grm.

The systematic use of neosalvarsan in a yaws community would, if thoroughly carried out, promptly get rid of the endemic disease, and, wherever possible, it should be enforced. The average time to effect a cure is given as eleven days. In Samoa it has been found necessary to give three injections of 0·6 grm. of neosalvarsan at weekly intervals for an adult male, and appropriately smaller doses for women and children. Babies are treated by intramuscular injections. Moss in San Domingo has found that the cure after three injections is permanent. The great objection to mass treatment of native populations with the salvarsan compounds is their prohibitive cost. Apparently, mercury and potassium iodide have little therapeutic action in yaws of adults as compared with syphilis, but in breast-fed children these drugs exert a curative action of absorption by the infant from the mother's milk.

II. Bismuth.—The successful treatment of syphilis by Fournier with sodium-potassium-bismuth tartrate has led to the adoption of a similar method of treatment in yaws. The considered opinion of workers is that none of the many bismuth preparations can be said to take the place of the synthetic arsenicals in African yaws and syphilis. The most active form appears to be the *sodium tetra-bismuth tartrate* in both secondary and tertiary yaws.

All preparations act more efficaciously when given in the early stages of the disease. Injections should be made deep into the subcutaneous fascia, and occasionally some induration and abscess-formation may result. When treating natives on a large scale, a soluble form of sodium-bismuth tartrate (*Sobita*),[1] the introduction of which we owe to J. O. Shircore, which is now manufactured locally in East Africa, is preferable ; 3 gr. dissolved in 3 c.c. of distilled water, or in oil, constitutes a suitable dose for an adult ; for children up to two years, ½–1 gr. ; from two to eighteen years, 1–2 gr. ; and aged persons 1½–2 gr. The generally accepted dosage for an adult is 1½–4 gr. weekly with a total dosage of 6–14 gr. Children tolerate relatively larger doses than adults. Since 1924, over a million cases have been treated in Tanganyika alone by this method.

In patients with septic mouths, stomatitis and albuminuria are

[1] This preparation is placed on the market by Howard & Sons.

liable to ensue as a result of this treatment. Other toxic effects are diarrhœa and skin rashes, while lassitude and articular pain occur in some cases. This has been one of the greatest objections to the general use of bismuth, especially in the Solomon Islands and the Congo, combined with the fact that three or more injections are necessary. On the whole the toxic effects of bismuth are less frequent and are milder than those of mercury and salvarsan. In Jamaica, the dioxide of bismuth is preferred and the next in favour is the oxychloride of bismuth. Bismuth salicylate is also used in 10-per-cent. suspension in olive oil. In Jamaica six to ten treatments are given. In the waging of a great anti-yaws campaign, as at present in Kenya and Tanganyika Territory, bismuth has the undoubted advantage of cheapness, costing less than half a farthing a dose. According to Hanschell, stomatitis may be avoided if the injection is made into the deep subcutaneous tissues rather than intramuscularly, and the resulting pain may be mitigated.

Bismostab (Boots) is metallic bismuth suspended in glucose solution. When given deep subcutaneously, it is practically painless. The dosage is 20 cg. (3 gr.) locally, and a total of 6 grm. (90 gr.) can be given altogether in refractory cases. In the tropics, however, preparations of bismuth metal have been abandoned as they are liable to block the needles.

Casbis (Bayer), a sterile oily suspension of bismuth hydrate in fine dispersion, is highly spoken of on account of the fineness of the suspension. Adults receive 0·5 1 c.c. doses, and the total dosage is 12–15 c.c.

III. Combined treatment.—According to the latest reports the combined *neo-bismuth* treatment is the most effective. By combining bismuth and neosalvarsan (neoarsphenamine) in alternating weekly injections, the chances of severe reactions are reduced. The neosalvarsan is given intravenously and the bismuth intramuscularly. Attempts to combine the two preparations in one compound are now being made. *Bismuth arsanilate* (Martindale) in sterules containing Bi_2O_3 53 per cent., arsenic 17 per cent., given by injection, has been tried in Tanganyika and Nigeria. Other preparations are known as *neotreparsenan* and *bismuth arsphenamine sulphonate*, 20 cg. (3 gr.) per week up to a total of 6 grm. (90 gr.). It is said that the addition of 0·1 c.c. of butyn exerts a local anæsthetic effect. The French preparation, which is well tolerated, is known as *Bivatol*.

IV. Arsenical preparations given by the mouth.—*Stovarsol*, which can be given by the mouth, is a much more convenient method of mass-treatment than injections of salvarsan. It is customary to commence with 1 grm. daily, increasing to 1½, 2, and 3 grm. on successive days for adults: ½–1 grm. for children. After a total amount of 8–15 grm., according to van den Branden and Lefrou, the Wassermann reaction becomes negative. Chesterman considers three doses only are necessary to effect a cure, but finds that he can give in

stovarsol ten times the corresponding dose of neosalvarsan. Slight diarrhœa is the only untoward symptom of intolerance occasionally observed, and he has given as much as 2 grm. to children at a single dose. One objection to stovarsol is that the full course may be more expensive than injections of salvarsan. *Halarsol* (May & Baker), oxyamino-phenyl-dichlorasine, in the form of intravenous and intramuscular injections in doses of 0·125 to 0·25 grm. for three doses at three- to four-day intervals, has been proved on the Congo to be efficacious in all stages of yaws. The minimal toxic dose is 4·5 mg. per kilo.

Carbarsone, *p*-carbamino-phenyl arsonic acid, first prepared by Ehrlich, contains 28·85 per cent. of arsenic. It is given in the same doses as stovarsol and the therapeutic dose is 75 mg. per kilo bodyweight.

Prophylaxis resolves itself into the adoption of measures to prevent contagion. These are the isolation and segregation of the affected; the dressing and treatment of wounds in the hitherto unaffected: the application of antiseptic ointments to yaws sores, so as to obviate the diffusion of germs; the purifying or destruction by fire of houses or huts notoriously infected; the prevention of pollution of bathing-water by yaws discharges; and, especially, the prompt treatment of the infected by salvarsan, bismuth, etc.

CHAPTER XXXIII

MYCETOMA AND BLASTOMYCOSIS

Synonyms.—Madura Foot; Pseudactinomycosis.

Definition.—A fungous disease of warm climates, affecting principally the foot, occasionally the hand, rarely the internal organs or other parts of the body. It is characterized by enlargement and deformity of the part; an oily degeneration and general fusion of the affected tissues. The disease runs a slow course, is never recovered from spontaneously, and, unless removed, terminates after many years in death from exhaustion.

History and geographical distribution.—It was first described by Kämpfer in 1712. Subsequently it was confused with tuberculous disease. Carter, from 1865 to 1874, furnished the information upon which modern descriptions of the disease are based. Much further information has since been supplied by Bouffard and Brumpt.

In India, mycetoma is endemic in widely scattered districts, although whole provinces, as that of Lower Bengal, enjoy an almost complete immunity. It appears to be acquired only in rural districts, the inhabitants of the towns being exempt. Among the more afflicted districts may be mentioned Madura—hence the name "Madura foot" by which mycetoma is often known—Delhi, various places in the Punjab, Kashmir and Rajputana. In recent years we have had accounts of its occurrence with some degree of frequency in Senegambia, Somaliland, Aden, Algeria, Egypt, the Sudan, Madagascar, Cochin-China, Italy, the United States, and South America. The following varieties have been described:—

i. Actinomycotic Mycetoma

Caused by the ray-fungus, *Discomyces bovis* (Harz, 1877). Actinomycosis has a world-wide distribution and is a common disease of cattle. It destroys bone by erosion and spares only nerves and tendons. The pus from the affected region contains small yellowish granules ("sulphur grains") of irregular shape, attaining at most 0·75 mm. in diameter. They are soft and consist of an inextricable felted mass of mycelium. The threads are radially arranged at the periphery of the grain, and their free extremity widens into a bulbous, club-like termination (10–20 μ long by 8–10 μ wide). These clubbed ends have been looked upon by several authors as forms of degeneration.

ii. Vincent's White Mycetoma

Caused by *Discomyces maduræ* (Vincent, 1894). This kind of mycetoma is common and widely distributed. It has been observed in Algeria, in Abyssinia, in Somaliland, in Cyprus, in India, in Argentina, and in Cuba. Unlike *D. bovis* and other mycetoma-producing fungi, it does not destroy bone, and does not seem to act directly on the general health of the patient, though ultimately and indirectly it may bring about cachexia.

iii. Nicolle's White Mycetoma

Caused by *Sterigmatocystis* (*Aspergillus*) *nidulans* (Eidam, 1883). So far, only a few cases have been observed, by Nicolle and Pinoy, in Tunis, but probably it occurs in many places, the parasite *S. nidulans* being widely distributed. Primary infection probably takes place from barley grain. The grains formed by this fungus may also attain the size of a pea, but they differ from those of *Discomyces maduræ*, inasmuch as they are more or less spherical and present a smooth surface.

iv. Bouffard's Black Mycetoma

Caused by *Aspergillus bouffardi* (Brumpt, 1906). The grains are quite characteristic. They are black in colour and vary in size from a pin's head to that of No. 1 shot. They present a mulberry-like surface which is smooth and glossy, the structure consisting of a coiled-up mass.

v. Carter's Black Mycetoma

Caused by *Madurella mycetomi* (Laveran, 1902). This mycetoma has a very wide distribution. It has been observed in Italy, in Africa (Senegal, French Sudan), and in India.

The grain formed by *Madurella mycetomi* is dark-brown or black in colour. It measures 1 to 2 mm. in diameter, is hard and brittle ; its surface is irregular and frequently presents pointed eminences which differentiate it from the larger and smooth grains of *Aspergillus bouffardi*. The grain is composed of white threads, always over 1 μ in diameter and attaining at times 8 to 10 μ, which secrete a dark-brown substance that cements them together.

vi. Brumpt's White Mycetoma

Caused by *Indiella mansoni* (Brumpt, 1906). This form was described from a specimen of Indian origin in the museum of the London School of Hygiene and Tropical Medicine.

The grains peculiar to this form are hard, white, and very small, varying in size between $\frac{1}{3}$ and $\frac{1}{4}$ mm., and having a lenticular shape. Some are bean-shaped and flat. To study their structure it is necessary to boil them first in a solution of caustic potash. The hyphal threads are large and closely set, but without any cementing substance between them. The periphery of the grain contains numerous large chlamydospores having thick walls and being full of protoplasm.

vii. Reynier's White Mycetoma

Caused by *Indiella reynieri* (Brumpt, 1906), originally described by Reynier from a specimen in Paris; a second case has been recorded from Greece.

The grains may attain 1 mm. in diameter; *they are soft, white, and consist of a coiled-up strand which gives them a peculiar appearance resembling the excrement of earthworms.*

viii. Bouffard's White Mycetoma

Caused by *Indiella somaliensis* (Brumpt, 1906). This form is perhaps even more common in India than Vincent's white mycetoma. Bouffard has found it twice in Somaliland.

Indiella somaliensis is a most destructive fungus. In a foot examined by Brumpt all the muscles, tendons, and bones had been replaced by sclerosed tissues more or less homogeneous and presenting numerous sinuses full of yellowish grains clustered together like fish-roe, and many small inflammatory nodules containing one or more grains.

Pathology.—On cutting into a mycetomatous foot or hand the knife passes readily through the mass, exposing a section with an oily, greasy surface, in which the anatomical elements in many places are unrecognizable, being, as it were, fused together, forming a pale, greyish-yellow mass. The bones in parts have entirely disappeared; where their remains can still be made out the cancellated structure is very friable, thinned, opened out, and infiltrated with oleaginous material. Of all the structures, the tendons and fasciæ seem to be the most resistant.

The most remarkable feature revealed by section is a network of sinuses and communicating cyst-like cavities of various dimensions, from a mere speck to a cavity an inch or more in diameter. Sinuses and cysts are occupied by a material unlike anything else in human morbid anatomy. In the black varieties of mycetoma this material consists of a black or dark-brown, firm, friable substance which, in many places, stuffs the sinuses and cysts; manifestly it is from this that the black particles in the discharge are derived. In the white varieties the sinuses and cysts are also more or less stuffed with a white or yellowish roe-like substance, evidently an aggregation of particles identical with those escaping in the corresponding discharge. In the very rare red variety the colour of the accretions is red or pink.

Under the microscope the mycotic elements can be readily recognized in the concretions. In microscopic sections of the tissues, evidences of extensive degenerative changes, the result of a chronic inflammatory process, can be made out. An important feature is a sort of arteritis obliterans, or extensive proliferation of the endothelium of the arteries, and, according to Vincent, a thickening of the adventitia of the vessels as well as of the capillaries in the more affected areas.

Symptoms.—Mycetoma begins usually, though by no means invariably, on the sole of the foot. The first indication of disease is the slow formation of a small, firm, rounded, somewhat hemispherical, slightly discoloured, painless swelling, perhaps about ½ in. in diameter. After a month or rather more, this swelling may soften and rupture, discharging a peculiar viscid, syrupy-looking, oily, slightly purulent, sometimes blood-streaked fluid holding in suspension certain minute, rounded, greyish or yellowish particles often compared to grains of fish-roe. In other examples of the disease the particles in the discharge are black, having the size and appearance of grains of course gunpowder. Sometimes these particles are aggregated into

larger masses up to the size of a pea. In time, additional swellings, some of which break down and form similar sinuses, appear in the neighbourhood of the first, or elsewhere about the foot (Fig. 85).

Fig. 85.—Mycetoma of about two years' standing. (*After Legrain.*)

The sinuses are mostly permanent, healing up in a very few instances only. Gradually the bulk of the foot increases to perhaps two or three times its normal volume (Fig. 86). There is comparatively

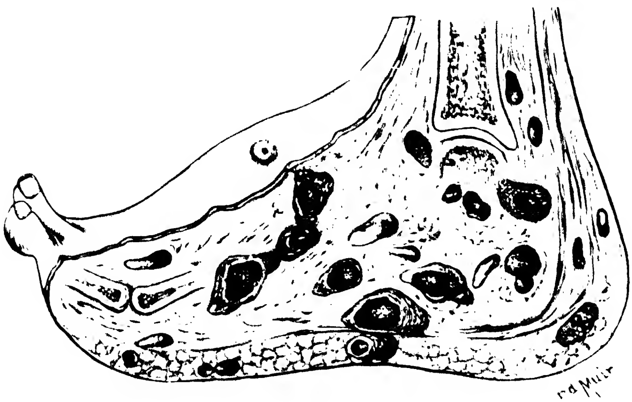


Fig. 86.—Section of a Madura foot. (*T. R. Lewis.*)

little lengthening of the foot; but there is a general increase in thickness, so that in time the mass comes to assume an ovoid form, the sole of the member becoming convex, the sides rounded, and the anatomical points obliterated. The toes may be forced apart, bent upwards at the tarso-phalangeal joints, or otherwise misdirected, so that when the foot is placed on the ground the toes do not touch it. The surface of the skin is roughened by a number of larger or smaller, firmer or softer hemispherical elevations, in some of which the orifices of the numerous sinuses open.

The discharge issuing from the sinuses differs in amount in different cases, and from time to time in the same case: whether profuse or scanty, it always exhibits the same oily, mucoid, slightly purulent appearance, and may stink abominably. With a very few exceptions it contains either the grey or the black grains already referred to; rarely, similar bodies of a reddish or pink colour.

As the foot enlarges, the leg atrophies from disuse; so that in the advanced disease an enormously enlarged and mis-shapen foot, flexed or extended, is attached to an attenuated leg consisting of little more than skin and bone. In some cases the tibia or, if the hand is the seat of invasion, the bones of the forearm are involved: in others the disease at first may be confined to a toe, or a finger, or other limited area. In a very few instances the seat of the disease is the knee, thigh, jaw, or neck. Unless the case be one of actinomycosis, the internal organs are never specifically implicated, either primarily or secondarily. The lymphatic glands likewise, although they may be the subjects of adenitis from secondary septic infection, are very rarely involved.

After ten or twenty years the patient dies, worn out by the continued drain, or carried off more suddenly by diarrhœa or other intercurrent disease.

Treatment.—The only effective treatment in the case of implication of a considerable part of the foot or hand, is amputation. This must be performed well above the seat of the disease; for it must be borne in mind that the long bones may be implicated as well as the small bones, and that, unless the entire disease be removed, it will recur in the stump. Complete removal is not followed by relapse. If a toe, or a small portion of the foot or hand, is alone involved, this may be excised with success. Potassium iodide in large doses has been found beneficial in certain forms of the disease.

Buchanan recommends surgical removal of as much diseased tissue as can be conveniently reached. Then tincture of iodine should be injected into any suspicious area remaining in the hope that the surviving elements would be killed; therefore 1–2 c.c. of iodine should be injected every ten days for a period of at least two months. At first the local reaction is not severe, but later it becomes so. Probably a less irritating solution, such as Lugol's solution, would do better.

Potassium iodide should be given by the mouth in large doses over

a considerable period, and there are those who think that the French tincture of iodine is more effective if administered in frequent doses of 2 drops in milk. Quite recently, the sulphanilamides—uleron and M. & B. 693—in full doses have been found effective in actinomycosis of the bowel, and therefore should be given a therapeutic trial in Madura foot.

Mossy Foot

The term "mossy foot" was applied by Wolferstan Thomas to a papillomatous condition of the feet and legs which is found occasionally in natives of the Amazon valley and its tributaries.

A similar condition has been described from Honduras and in East Africa (Fischer). The foot and ankle are covered with dense warty-looking out-

Fig. 87.—Mossy foot. (*By courtesy of Wellcome Bur. Sci. Res.*)

growths resembling minute barnacles, which are vascular and painful. In general appearance the condition has been compared to dry moss growing on rocks (Fig. 87). Some of the cases described are apparently *dermatitis verrucosa*.

The sole of the foot usually escapes. The disease is infective, and auto-inoculation from one limb to another may apparently take place. Starting as a vesicle, the growth slowly extends from the dorsum to the hinder part of the foot, and is said to take ten years to develop fully. It can be inoculated into the nose in rabbits, and produces in them a verrucoid mass at the site of inoculation.

Ætiology.—The disease is said to be due to an infection of the skin with a fungus, *Phialophora verrucosa* Thaxter, 1915, which was specially studied by Pedroso and Gomes in Brazil in 1920. This fungus can be cultured on ordinary media, and forms a brownish-black growth. Stab-cultures in ascitic agar and serum form, in the depth of the medium, nodules analogous to those in the tissues. On these media, chlamydospores 8–15 μ in diameter, as well as conidia, are produced, and sometimes aërial hyphæ develop.

According to Medlar, yeast-like cells can be seen in sections of the tissues. Mackinnon (1934) has described a case in a European in Uruguay as *chromoblastomycosis.* The lesions on the patient's right hand resembled sporotrichosis, from a histological point of view. It is claimed that *P. verrucosa* is the cause of chromoblastomycosis, and as far as is known, its distribution is Brazil, Paraguay, Porto Rico, the southern United States, and North Africa.

The general opinion in regard to the ætiology of mossy foot is, however, somewhat sceptical, because a similar warty condition of the epidermis is apt to occur in patients suffering from elephantiasis, and also from yaws. On the other hand, Delamare, Gatti, and Gonzalez described a very similar condition in South America produced by cutaneous leishmaniasis, especially of the dorsum of the foot. The lesions consist of papillomatous outgrowths or vegetations of a cauliflower character, usually a single patch which may cover the entire dorsum of the foot, but sometimes patches are to be found on the heel or side of the foot and on the toes; the vegetation may be hard or soft according to the degree of keratosis which has taken place.

Treatment.—In Thomas's experience, the best treatment is the actual cautery.

Blastomycosis

This term is used to indicate lesions, other than mycetoma, produced by the proliferation of certain yeast-like fungi in the tissues. Normally these fungi are either saprophytic or live as parasites on animals or plants, and appear to be especially abundant in tropical countries. Doubtless they get access to the human tissues through some wound or breach of surface. The following clinical types have been recognized:

1. **Cutaneous.**—Patches, of various dimensions, of small warty excrescences with minute abscesses or encrusted ulcers, especially at the periphery of the patch.

The most important of these cutaneous infections is coccidioidal granuloma, or Posada's Disease (Rexford and Gilchrist, 1894, first discovered in Buenos Aires by Wernicke in 1892). It has been found especially in Brazilians, in whom it causes extensive ulceration. The pus from the lesions is easily inoculated into animals, especially guinea-pigs, in which it causes a virulent infection. Up to 1931, 286 cases had been reported, usually in Upper California, and it has also been seen in oxen there. Infection of man is probably caused by inhalation of the spores, and the skin lesions originate round the site of scratches and other lesions.

The organism concerned is *Coccidioides immitis.* It produces acute, subacute or chronic manifestations with cutaneous, subcutaneous or systemic lesions, generally involving the respiratory system. The lesions themselves may be nodular, ulcerative, papillomatous, or verrucous, resembling a gummatous tumour or cold abscess. The cells of Coccidioides occur either isolated or in giant cells. They are spherical and thick-walled with a diameter of 2–80 μ. The organism reproduces by endospore formation; budding is absent. The wall of the ascus often shows radiate formation. The colonies on culture are flat, and greyish in colour, becoming white to light cream, with aërial hyphæ, which in microscopical appearance are septate, branching, hyphal swellings; arthrospores, 2·5–7 μ in diameter; chlamydospores are abundant 5–8 μ in diameter. Studies in metabolism of *C. immitis* show that the organism is resistant to desiccation, but the chlamydospore develops under conditions of drying, and it is impossible to infect animals in the absence

of this spore. This resistance to drying is an important factor in dissemination of the organism in the San Joaquin valley of California.

The cutaneous type of blastomycosis also includes the following conditions :

North American Blastomycosis or Gilchrist's Disease (1894) (*Zymonema dermatitidis*).—An infectious granuloma, acute or chronic, with cutaneous or systemic lesions—papulo-ulcerative, verrucous, or papillomatous, or gummatous, showing typical violet colour. The organism has simple or budding yeast-like cells, thick-walled and 5–20 μ in diameter ; the colonies on culture are yeast-like. Hyphæ are septate and branching, 2–4 μ in diameter ; conidia are pyriform or round, 5 μ in diameter.

European Blastomycosis (*Cryptococcus hominis*) is clinically similar to Gilchrist's disease, but an ulcerative type is common in the cutaneous form, with abscesses, and quite commonly invades the cerebro-spinal system as well. The organism has thick-walled, heavily-encapsuled, simple or budding cells, 5–10 μ in diameter. Colonies on culture are " yeasty," smooth, mucoid or moist, and spherical or ovoid with budding encapsulated cells approximately 2–6 μ in diameter.

South American Blastomycosis, or Splendore de Almeida Disease (Lutz, 1908) (*Paracoccidioides brasiliensis*), is generalized or localized, cutaneous or systemic, the lesions being granulomatous, papular, verrucous or ulcerative. It spreads by the lymphatics. The cells are spherical or ovoid, 1–30 μ in diameter, rarely larger, with thick walls.

2. **Oral.**—Lesions resembling those described under the cutaneous type, which develop in or spread to the mucosa of the mouth and throat, and eventuate in deep ulceration and perhaps fatal destruction of the part. A form occurs on the tongue, leading to hypertrophy of the filiform papillæ, and causing a condition known as *lingua nigra*. The organism is known as the *Cryptococcus linguæpilosæ* ; it has a double contour, is composed of oval yeast-like cells and mycelia elements, and can be cultivated on maltose-agar.

3. **Pulmonary.**—A parasite—*Cryptococcus capsulatus*—allied to *C. farciminosus* of the horse, has been demonstrated in the epithelial cells of the lung by Darling. The disease it produces resembles in many respects kala-azar, and is accompanied by splenomegaly, anæmia, irregular pyrexia, and leucopenia. Three cases have been described in Panama. Crumwise and Kessel (1932) have described a case of the condition in which splenomegaly did not occur. The organism was originally named *Histoplasma capsulatum* by Darling in 1906.

Niño in Argentina has described as *Cryptococcus psychrophylicus* an organism which caused a generalized infection originating from an ulcerated condition of the face. The organism grew best at 22–25° C., but was arrested at 37° C. Guinea-pigs, white mice, and rats were susceptible to inoculation.

4. **Sporotrichosis.**—Gumma-like swellings in limbs or trunk, which enlarge and ultimately break down, leaving deep ulcers, due to an organism, *Sporotrichum* (*Rhinocladium*) *beurmanni*, or *S. schenckii*, which usually exists saprophytically, and gains entrance to the body through an abrasion of the skin or œsophagus. Occasionally the organism may be demonstrated in the blood ; the lymphatics, eye, oral cavity, periosteum, muscles, or viscera may become involved. In the discharges and tissues the parasites are scanty, so that the mycotic nature of the disease can be made out only from cultures. Benham and Kesten isolated the organism from linear nodules in a man's arm, and reproduced the lymphatic type of infection in a monkey. Inoculation of white rats produced typical orchitis.

Pijper and Pullinger (1927) have recorded 14 cases in native miners on the South African Rand. They distinguish a primary sore in the form of a localized ulceration on a finger, or the shin. Ten of the fourteen cases had the lesions confined to one arm, the others on the shin, with the lesions extending up the leg as high as the buttock. Incision of the nodules in the paths of the lymphatics produced pus or serous fluid.

Sporotrichum beurmanni can be isolated from the tissues by aspiration and insemination on to Sabouraud's medium. The parasite occurs in wild rats in Argentina and Brazil, while a similar disease, apt to be mistaken for epizoötic lymphangitis, occurs in horses and mules in Madagascar (Carougeau).

It appears to be a common parasite in nature, and recently (1933) Benham and Kesten have transmitted the human parasite to carnations, in which it produces a " bud rot " similar to that caused by a natural parasite, *S. poæ*.

The parasitic elements are very scanty in the pus, and in mycelial elements are seen either in sections or in cultures. Individual parasitic elements are often found engulfed by phagocytes.

5. **Torulosis.**—This gives rise to grave lesions of the pulmonary and nervous systems, and local tumours of a peculiar consistency containing round cells surrounded with a gelatinous substance secreted by the organism. The parasite of this condition, which has been especially studied by Kessell in California, is known as *Torulopsis histolytica* (Stoddard and Cutler, 1916), or as *Torula histolytica* or *Cryptococcus histolyticus*. It is usually found in the cerebro-spinal fluid. Experimental infections are easily produced in rats and mice by intraperitoneal injection, generalized lesions being produced in lungs, liver, spleen, kidneys, and brain. Kessel and Holtzwart find that 45 cases have been reported in the literature: most have involved the central nervous system and four have exhibited a general infection. In four other cases the infection was localized to the muscles of the vertebral column, to pelvic and inguinal abscesses, or to the tongue or naso-pharynx. In one of the cases from Los Angeles the lesions were confined to the knee. This disease appears to be incurable. The diagnosis is usually made by cerebro-spinal puncture.

T. histolytica is a primitive form of yeast cell: it multiplies by gemmation, and can be cultured in glucose broth or on Sabouraud's medium. The colonies are glistening white, and show no mycelia penetrating into the substratum, as is characteristic of Monilia. The individual cells multiply by gemmation only, no hyphæ being observed. The cells themselves exhibit characteristic capsules. No asci are formed.

The sugar reactions are typical: no acid or gas is produced in arabinose, dextrose, galactose, inulin, maltose, mannitol, raffinose, sucrose, lactose or dextrin. The reaction in milk is alkaline. When inoculated intraperitoneally into rats and mice, the animals die in eight to twenty-eight days, and the organisms can be recovered from the tissues. Monkeys inoculated intra-cardially develop small nodular cutaneous lesions on the face, eyelids and ears containing the organism. In some monkeys, however, a general torulosis of the brain and spinal cord develops.

Diagnosis.—Usually the lesions of blastomycosis in the first instance suggest syphilis or tuberculosis. Specific treatment and absence of reaction to tuberculin and of the tubercle bacillus should lead to a careful search for yeast-like organisms in the discharges or scrapings. Widal and Abrami have found that the serum of sporotri-

chosis will agglutinate cultures of the specific organisms ; while Malvoy and Ricketts have demonstrated a complement-fixation test in blastomycosis, using an old culture as an antigen. Martin (1935), especially, has employed this method in diagnosis. The antigen employed has a suspension in salt solution of the organisms grown at 37° C. on beef-infusion, *p*H 7·4, on blood-agar slants. The patient's serum was inactivated at 56° C. for fifteen minutes, and the test was carried out as for the Wassermann.

Treatment.—All forms of blastomycosis are exceedingly chronic and resistant to treatment. Surgical measures are useless, but large doses of the iodide of potassium or of sodium (20–30 gr. three times a day, well diluted) are sometimes effective, and should always be tried and, if found beneficial, continued until cure is well established. In sporotrichosis the tumours can be punctured and injected with potassium iodide 1 : 100, while treatment must be continued for some time after an apparent cure has taken place. The X-rays are at times a useful adjunct.

Section V.—DISEASES OF THE CENTRAL NERVOUS SYSTEM

CHAPTER XXXIV

NEURASTHENIA IN THE TROPICS

For some time past the Editor has been aware that in a textbook of Tropical Diseases attention must be paid to this important subject, as the minor psychoneuroses play no inconsiderable part in adding to the burdens of life in the tropics, and are the cause of a proportion of invaliding among European officials and business men from the tropics ; more especially is this the case in West Africa. As a cause of disability, neurasthenia or anxiety psychoneurosis, or whatever term may be applied to this very real and distressing condition, has superseded that from tropical disease. Therefore from the practical point of view of Colonial Administration, neurasthenia is of greater importance than the majority of the tropical diseases with which this textbook purports to deal. As observers who have displayed a more than cursory interest in this condition know, there is nothing essentially peculiar to tropical neurasthenia which should serve to differentiate it from similar anxiety neuroses developed by a similar class of person resident in temperate climates and subjected to stresses of various kinds.

When it is considered that from the figures available quoted by Squires, no less than 45 per cent. of a total of 353 invalidings of Europeans from the tropics were due to psychological reasons, there is obviously some feature in life under tropical conditions which predisposes towards this psychological state. Naturally, fully developed and frank neurasthenia, as seen in its most characteristic form, is more apt to develop in a neurotically-disposed individual than in one of a complacent and unemotional mental make-up, and it is not always possible to be able to gauge, with any degree of accuracy, those individuals in whom tropical neurasthenia will eventually develop. It has even been asserted by Culpin that a certain number of persons actually avail themselves of the opportunity of going to the tropics as a flight from the strain of social life at home.

The influence of tropical infections (p. 17).—The Editor believes that tropical infections, especially the enervating, debilitating, and irritating recurrent relapses of subtertian malaria, are potent predisposing factors to this psychological state. The recurrent headaches and fevers result in

referring sensations to the cranium, causing neurasthenic headache, lack of concentration, loss of memory (West Coast Memory), and general disinterestedness in life. The intestinal infections, such as amœbic or bacillary dysentery, may result in a concentration of thought and effort on the intestinal tract. The patient's attention becomes rivetted on his digestive system, with the result that an intestinal psychoneurosis develops. Therefore in this respect tropical infections do undoubtedly predispose to "tropical neurasthenia." But there are other aspects of life in the tropics which engender self-introspection. The heat, insect life, the proximity to natives who cause him annoyance at every turn and whose ways and psychology he cannot understand, the dull monotony of life, the ever-recurring twelve hours of daylight alternating with twelve hours of pitchy night, the howling of dogs, the croaking of frogs and the abundant and vexatious insect life; all these act as stimuli which goad him on to the neurasthenic state. The dulling of the appetite engendered by heat, the unpalatibility and unsuitable nature of the food, the greasy cooking, the abundance of starchy matter in the food, the monotony of eating tinned foodstuffs, together with the comparative absence of essential vitamins, by which the food is characterized, all tend to upset the digestive apparatus and to act as a depressing factor on the higher psychical centres.

Sleep.—In the Editor's opinion insomnia, which appears to be the outward manifestation of physical exhaustion and which nearly always appears towards the end of the tour in tropical Africa, is usually the first manifestation of the neurasthenic state; and in order to prevent the psychoneurosis from becoming a permanent feature, rapid invaliding to a temperate climate becomes necessary.

Sexual factors, etc.—Other factors have been adduced to account for this psychoneurosis, and these present themselves to anyone who has lived in isolation under tropical conditions. There is the sex factor which may in some individuals be a potent one; there is again the social isolation which operates in out-stations; in others it is excess of alcohol, late hours, or living a life attended by native servants under conditions to which he had been so far unaccustomed—all these may be adduced as factors which may upset the mental equilibrium. Then there is, too, absence of restraint in offending local prejudices and the added example of others similarly placed.

Work and exercise.—It is probable that hard mental and physical work, in moderation, act as a bar rather than as a predisposing factor in the development of neurasthenia. Mental occupation of a moderate degree tends to divert the mind from self-concentration. On the other hand mental pressure or undue stress appears to be less easily tolerated in the tropics than at home; so it must not be thought, in searching for essential factors in this state, that neurasthenia is a special mental affliction of Europeans, for neurasthenia of the depressive type is frequently observed amongst the educated native officials in West Africa, Malaya, India, etc., though the proportion is by no means so great as in Europeans.

Neurasthenia in women.—It is difficult to state the proportion of neurasthenics in both sexes; it is probable that women, with their more highly developed emotional centres, are more prone to develop this state, granted equal opportunities, than men.

A tropical climate usually produces certain psychological effects in women. Such women who become neurasthenic suffer from pelvic pain and discomfort, loss of blood at the periods and toxæmia; in short, much the same things which make for neurasthenia in temperate climates. For women, life under

tropical conditions predisposes to underlying conditions which produce these symptoms. Constipation, by favouring pelvic congestion and inflammation, and uterine displacements have also to be considered.

The effect of the tropical climate on the newly-arrived European woman is at first distinctly exhilarating. The appetite is increased and the heat does not oppress her at first as it does in succeeding years, and there is a distinct feeling of well-being. Menstruation frequently stops for a season and then naturally re-establishes itself. The sense of well-being may be so real that risks are taken which more experienced residents avoid, such as the eating of unsuitable food. The long hours that European ladies spend in shaded houses during the heat of the day engender a feeling of lethargy, due to extra work being thrown on the liver, and partly due to want of exercise. Congestion of the liver, and constipation, which especially has a depressing effect on the mind, may result, and in this connection neurasthenia develops, which is not primarily a pelvic disease but which is intimately connected with it.

Childbirth in European women in the tropics is apt to be more difficult and laborious than in temperate climates, due very probably to the conditions under which most live; but even among native women something between 30–40 per cent. of deaths are directly or indirectly connected with parturition. Native women, as a rule, parturate with extraordinary ease, and it is only in those countries where women have departed from a natural mode of life, and are living in seclusion, that parturition is by no means a simple process.

The effect of tropical conditions.—Tropical life has a disturbing effect upon the mentality of even the most healthy and sanely-balanced individual. After a year or more of constant exposure to heat and humidity, the hours of sleep become disturbed, and the nervous system more sensitive to external stimuli. For the precipitation of insomnia, certain electrical conditions of the atmosphere at present little understood, skin conditions, especially prickly heat, and possibly a hyperglycæmia which Dutch investigators in Java ascribe to the climate, may be at fault. It is a common experience to find otherwise healthy adults to be "nervy" and "excitable," showing exaggerated reflexes and nervous twitchings of the face and limbs, with increased reflexes, directly they return to a temperate climate. In the minor states of disturbance the fears and stresses disappear the moment cool head-winds are encountered, and peaceful and refreshing sleep is enjoyed once more. But to the fully-developed neurasthenic transference to his home climate does not immediately relieve him of his fears: on the contrary, the sounds and stirring of traffic and the hum and bustle around him act as further stimuli to accentuate the neurasthenic state.

The effect of quinine.—In certain individuals the constant absorption of quinine for prophylactic purposes has a depressing effect upon the mentality. It may be a direct mental depressant; on the other hand, it may act indirectly by causing indigestion and abdominal discomfort. This subject has been discussed under the heading of "Quinine Prophylaxis," and it is open to question whether more harm, in the neurasthenic sense, is not done by constant taking of quinine, than is counterbalanced by such protection as the practice affords.

Symptoms.—The symptoms of neurasthenia in the tropics are usually not difficult to assess. The very appearance of the individual betrays his mental state. He (or she) is emotional to a degree, so that any sympathetic reference to health may provoke a flood of tears. There are others in whom the most

profound depression reigns, and who may display suicidal tendencies ; these are usually associated with intractable insomnia.

The patient usually complains of a headache which is confined to the temporal regions or the parietal portion of the cranium. There is a sense of increased intracranial pressure. There are others who complain of a sinking feeling in the abdomen, or indefinite abdominal pain, or flatulent dyspepsia. There is usually a mild degree of tachycardia, or rather vasomotor instability —a fall in blood-pressure with a diastolic pressure below 80. The reflexes are usually exaggerated and there may be a false ankle-clonus with hyperidrosis of the palms of the hands and of the feet.

It has been suggested that the main symptoms are to be ascribed to hyperthyroidism, but the Editor has been unable to find any evidence for this hypothesis. With this degree of nervous instability it is not surprising to find divergence of the pupil on accommodation (Mœbius' sign) which by some is considered to be indicative of hyperthyroidism. Of course it is necessary to distinguish neurasthenia from true hyperthyroidism, especially of the substernal variety.

Treatment.—The main principle in treatment is to remove the patient from his immediate surroundings to a temperate climate with congenial companions. Usually, on arriving in a cool climate, natural sleep sets in and his groundless fears and anxieties disappear. The neurasthenic state may be a temporary one only. On the other hand, the emotional and depressive states should be treated seriously and efforts should be made to discover some underlying infection. The Editor has seen on several occasions profound neurasthenic symptoms disappear after treatment of an underlying unsuspected malaria. If alcohol has been taken in excessive amount, the amount must be cut down or prohibited altogether. Efforts should be made to divert the patient's attention from himself. Hobbies of all kinds should be encouraged and there is probably no occupation more restful and curative than fishing in the Highlands of Scotland or in Ireland.

For insomnia, hypnotics of the milder type should be prescribed, such as allonal, luminal, or medinal. Sleep may be induced by such methods as a hot bath or a cup of Ovaltine. As a general sedative a mixture of the following type may be prescribed to be taken three times daily :

Ammon. brom.	gr.x	(0·648 grm.)
Spirit. ammon. aromat. . .	♏xv	(0·888 c.c.)
Tinct. ergot. ammon. . .	♏xx	(1·184 c.c.)
Syrup. aurant.	ʒi	(3·55 c.c.)
Aq. menth. pip. ad . . .	℥ss	(14·21 c.c.)

℥ss three times a day after meals.

Prophylaxis.—As the main treatment of neurasthenia entails removal from immediate surroundings, its prevention is a difficult matter. Once marked neurasthenia has developed in a European in the Tropics, he should be invalided to a temperate climate and the question of his return to his position becomes a matter for anxious consideration. Of course there are cases in which the patient regains his mental equilibrium in a short space of time ; but should the mental depression continue in spite of the simple methods recommended, then permanent invaliding should be considered. The Editor is of the opinion that a patient with well-marked tropical neurasthenia should never be permitted to return, otherwise the old symptoms will reassert themselves directly he sets out, and after a few months he will be sent home again.

CHAPTER XXXV

ENCEPHALITIS JAPONICA

Synonym.—Japanese Type B encephalitis.

Encephalitis japonica is, strictly speaking, an epidemic encephalomyelitis involving the brain and spinal cord, and is to be distinguished from epidemic encephalitis (encephalitis lethargica) by the absence of eye lesions and other features to be detailed later.

Encephalitis japonica, as its name implies, is well known in Japan, where it apparently has occurred in epidemic waves since 1871. In 1933 it was found in different portions of North America (St. Louis; Toledo; Kansas City; Paris, Ill.; and St. Joseph, Mo.). In 1938 it was recognized by Pette as occurring in Germany and by Silberman in Vienna. In 1928 Kaneko and Aoki made an intimate study of the disease and were able to differentiate it from encephalitis lethargica and to determine its identity with *Encephalitis B.* In 1924 a very severe epidemic occurred in Japan during a very hot and dry summer season, when 7,000 cases were recorded with a mortality of nearly 60 per cent. This disease spreads rapidly, in a manner more nearly resembling poliomyelitis, more commonly and more severely attacking those over fifty years of age, in contrast to the relatively mild disease it produces in young people.

Symptomatology.—The prodromal symptoms commonly encountered are headache, dizziness, sluggishness, and vomiting. These are followed by psychical disturbances and very often by delusions, but in very severe cases coma ensues, ending in death. The psychical signs and symptoms may be entirely absent in the mild cases, and in contrast with encephalitis lethargica, meningeal symptoms predominate. Disturbances of the motor system are characteristic: there are clonic contractions of the muscles which may end in actual convulsions. Fine tremors of individual groups of muscles alternate with attacks of shivering and athetoid movements. The whole muscular tone is increased in the extremities and in the neck and face, especially the masseter muscles, which results in imparting an anxious expression to the face, and ends in trismus which renders mastication impossible. In very advanced cases, encephalo-myelitis causes paralysis of the spinal cord, but in direct contrast to encephalitis lethargica, eye symptoms are absent; nor is post-encephalitic Parkinsonianism ever observed, though bulbar symptoms, resulting in failure of speech and difficulty in swallowing are quite common and, in addition, defects in co-ordination and sometimes even cerebellar disturbances.

Anomalies of superficial and deep tendon reflexes are usually present especially in *spastic* cases.

Salivation and excessive sweating are absent.

The foregoing description covers only the main features, however; actually the clinical picture is a many-sided one. There is also another side to this disease in that, though the neurological aspect dominates the picture, there is a secondary affection of the hæmopoietic organs, resulting in a secondary anæmia, which appears to indicate that we are dealing with a generalized infection rather than a local affection of the central nervous system. As a rule, the temperature chart is not characteristic, and the course of the disease is generally afebrile. There are cases, however, in which fever is noted for five to ten days, and these are followed by sequelæ, such as profound neurasthenia. The fulminating cases which are fatal in twenty-four to forty-eight hours are generally pyrexial. It is to be noted that there are no pupillary or eye symptoms, and there is no special affection of the bladder or bowels. Usually there is retention at first, followed by incontinence.

Ætiology.—Our knowledge of the virus of epidemic encephalo-myelitis we owe to Kobayashi, Takaki, Nishibe and Hayashi. Credit is due especially to the latter for his important researches on its transference to monkeys, in which it produces the same histopathological lesions as in man. In America, however, white mice have been found more susceptible than monkeys. Webster and Fite have shown that the virus, which is active in the blood and in the central nervous system in the early stages of the disease, can be inactivated by convalescent serum.

The transference of the virus from man to man has not been ascertained with certainty, but it is to be noted that the virus of the somewhat similar encephalo-myelitis of horses (equine encephalo-myelitis), which causes a fatal and extensive disease in America, has recently been proved to be transmitted by certain mosquitoes.

Diagnosis.—The main points in differentiation from encephalitis lethargica have already been noted. The cerebro-spinal fluid shows all grades of inflammatory disturbance. Kaneko and Aoki have shown that there is an increase of the albumin content from 9–350 mgm. per cent.

Pathology.—Epidemic encephalo-myelitis is characterized by diffuse lesions in the brain and spinal cord. These take the form of small white knob-like aggregations of cells, composed of microglia intermingled with lymphocytes and leucocytes. Here and there ganglia cells also are found to be acutely damaged.

Treatment.—No specific treatment is at present known.

CHAPTER XXXVI

LÂTAH, RUNNING ÂMOK AND KORO

Lâtah, a word signifying "nervous" or "ticklish," is not uncommon in the natives of the Malay Peninsula, Java, and the neighbouring islands. It is apt to occur more frequently in women, especially young women, than in men; children are rarely affected; it rarely appears before puberty and is especially common at the menopause.

A somewhat similar affliction is described among the Ainu people, usually in women, and is known as *imu*. This manifests itself by psycho-motor attacks precipitated by some emotional shock. Thus, if one suffering from it is startled, she may continue to echo everything that is said to her.

Lâtah persists for years. The main characteristics of this psychosis are the same though there is considerable variety in the intensity of the symptoms. The condition is incurable and shows no tendency to become worse, and it does not terminate in insanity.

As the Malays say, an *orang latah* never becomes an *orang gila* (âmok). The subjects of "lâtah" at first appear to differ in no way from their neighbours and relations, but the occurrence of some sudden and striking impression, such as a loud sound, or in response to some overt suggestion by word or deed, they pass into a peculiar mental state in which they involuntarily utter certain sounds and execute certain movements. In other instances they will imitate words or movements, or yield themselves to suggestions coming from others. During this hypnotic-like state, which may last for a few minutes, or in others longer, the victim is at the mercy of his prompter and will unerringly follow any lead which is indicated. Although the manifestations of high degrees of lâtah may be followed by signs of exhaustion, or even by swooning, as a rule nothing of the kind occurs. The infirmity is usually discovered by accident. Swettenham, for instance, used to relate that it was only necessary for anyone to attract the attention of these men by the simplest means, such as holding up a finger, or calling them by name in a pointed way, touching them, or looking them steadfastly in the face, in order to make them lose control of themselves and be willing to execute whatever was suggested by a sign. On one occasion, one of them on being told that a roll of matting was his wife, embraced it with every sign of affection; but when the other lâtah subject, a policeman, was impressed that the same roll was his wife likewise, he too embraced it, and the two men fell to the ground struggling for the possession of the "lady."

Lâtah folk are favourite subjects for the practical joker, and in a few instances they very much object to be made a show of, and may become dangerous. Lâtah seems to be akin to a class of emotional stresses which are common in all barbarous and semi-civilized countries.

Abraham has seen the afflicted, if suddenly startled, fall down and imitate the gestures of anyone in sight; for instance, an old lady startled by a bicycle bell, will instantly imitate the pedalling of the cyclist till exhausted.

There appears to be a somewhat similar affection amongst the Samoyedes which is known as "Ikota," and it is believed that the curious epidemics of religious ecstasy which swept over Europe during the Middle Ages, were of similar origin. Unless unforeseen accidents occur, lâtah is not fatal. Gimlette and others have called attention to the medico-legal aspects of the disease. Fortunately examples in which lâtah has been shown to play a part in crime are rare. Temperamentally all the Malay races are very highly strung and nervous, although externally impassive, and there appears to be an hereditary tendency to the lâtah state in every Malay.

"**Amok**" (or running âmok) is a term used somewhat loosely for a condition which, in the fully developed form, drives its victims to blind fury and to kill without reason.

Usually the "âmok" runner (or âmoker) has a grievance upon which he allows himself to brood, and after a period of sullenness decides to kill the suspected person and at the same time to destroy as many other people as possible. He therefore arms himself and runs "âmok," and buries his *kris*, when out to slay, in friend and foe alike, with the expectation of being killed in turn.

In other cases there may be premonitory signs in which a person mutters and has delusions. Quite suddenly he will run "âmok" and after the attack may fall into a deep slumber and become comatose. The liability to "âmok" attacks is greatest in the Malays, and their drugs, such as Indian hemp (*Cannabis indica*) are known to be potent predisposing causes of the attack. Van Loon now finds that in Java "âmok" runners are often suffering from some infectious disease, and that the symptoms are of hallucinations and confusion: patients are impelled to flight and attack as reactions to imaginary dangers and the agony and terror caused thereby.

"**Koro**" occurs amongst the Macassars and the Buginese in Celebes, and is also well known among the Chinese as *Shook Jong*, originally described by Blonk in 1895. The term signifies "shrivelling," and in this condition a feeling occurs at regular intervals of the penis retracting into the abdomen; if help is not forthcoming, the patient dies. In his anxiety, the patient grasps the penis, and if unable to do so, obtains assistance from others. It may be days before the attack subsides, and the sufferer cannot bear to be left alone. If help be not to hand, he will actually tie the penis to his leg with string, anchor it by means of a pin, or may even employ a double-bladed clasping instrument known as *li teng hok*, which is employed by jewellers. By the native this tendency is regarded as the "Yin" principle, representing the female power, dominating the "Yang" principle, which represents the male element. In order that a "Yin" disease may be cured, a "Yang" medicine must be employed. The sufferers are generally neurotics, and the anxiety arises out of sexual conflicts. Various pathological conditions, such as œdema of the lower abdomen, hernia, hydrocele and elephantiasis of the scrotum may evoke fear of an attack. An analogous state, characterized by diminution of the genital labia and shrinking of the breasts, is known to occur in women.

Section VI.—TROPICAL VENEREAL DISEASES

CHAPTER XXXVII

CLIMATIC BUBO

Synonyms.—Lymphogranuloma inguinale; Inguinal poradenitis; Poradenolymphitis; Nicholas-Favre disease (French).

Definition.—A type of adenitis of venereal origin, of which the primary lesion occurs on the prepuce or male genitalia. The infection—a filterable virus—causes inflammation and, subsequently suppuration of the inguinal glands. This suppurative state is usually attended by pyrexia and general constitutional disturbance. The bubonic stage occurs in the male sex as a rule, and it is thought by some that a general lymphœdema with ulceration, known as esthiomène, represents the analogue in the female. Some authorities also consider that the genito-ano-rectal syndrome and inflammatory structure of the rectum are due to the same cause.

Ætiology, epidemiology, and geographical distribution.—Scheube originally applied the term "climatic bubo" to a type of adenitis terminating in suppuration, not uncommon in tropical countries. Whether it is becoming increasingly frequent, or whether it is because attention has been drawn to its peculiar nature in recent years is a moot point; but recently "climatic bubo" has emerged from the obscure recesses of textbooks on tropical medicine into the full limelight of general medicine, so as to merit the title of the "*Sixth Venereal Disease*" which has been bestowed upon it by Stannus.

In tropical practice climatic bubo is especially prevalent amongst the European crews of warships visiting the coasts of East and West Africa. In the Editor's experience it is almost equally common in seafaring people (lascars, stewards, and British sailors) throughout the whole of India, China, Malaya, Japan, the Mediterranean, West Indies, and South America.

In 1913, Durand, Nicolas, and Favre described the condition, which they termed "*lymphogranuloma inguinale*" in France, and possibly the condition long known as the "strumous bubo" is the same.

In 1933 Stannus and Findlay discovered an indigenous case in England; the Editor has seen two, and more recently Anwyl Davies discovered three more. Now numerous reports of its occurrence in Italy, Rumania, and in fact the whole of Europe, are to hand. In the United States, the disease in all its forms has been discovered, chiefly

in the coloured population. At certain times and places it appears to be epidemic. There seems to be no doubt, according to Rost and Ruge, that the disease is acquired from sexual connection with native women.

The virus.—Hellerström and Wassén (1930) originally transmitted the virus obtained from the pus of inguinal buboes to monkeys; intracerebral inoculation produced meningo-encephalitis. The virus, which is apparently contained in the leucocytes, consists of minute particles which can be easily seen, and have been figured by Findlay (1939). They can be stained by Victoria blue, Giemsa or Castanêda's method; with Giemsa, the larger bodies take on a bluish-purple tint, while with Castanêda's stain they are reddish-purple. Larger and smaller forms of the virus particles can be demonstrated outside the cells, lying close to cell débris, in the form of compact colony-like masses. When they are within cells, the elementary bodies may be found in the cytoplasm of either mononuclear or polymorphonuclear leucocytes. Occasionally these groups may attain considerable size, forming cyst-like spaces: later the cyst-wall may rupture. The larger forms have been observed in considerable numbers, chiefly within twenty-four hours of intracerebral inoculation. There therefore appears to be a developmental cycle of the virus which is completed in forty-eight hours. The virus particles or granules were first described in cells from inguinal buboes by Gay and Prieto in 1927, and similar bodies were found by Findlay in 1933. Miyagawa (1938) finally stated that they constituted the virus and gave their measurements as 0·125–0·175 μ while Findlay, Mackenzie and MacCullum maintain that they resemble similar bodies found in psittacosis by Bedson and Bland in 1932. The only other condition in which these bodies have been observed is inclusion conjunctivitis, and it is possible that they are allied to the *Rickettsia*.

Intraglandular injection of guinea-pigs with the virus produces an inguinal bubo in almost every case, so that this method may be employed for diagnosis. The most reliable method at present is Findlay's intracerebral inoculation of white mice, which produces an encephalitis. Miyagawa has now found that a chipmunk, *Eutamias asiaticus*, is highly susceptible to intratesticular and intracerebral inoculation. The virus can also be cultivated in chick chorio-allantoic membrane in tissue culture. Ravaut, Levaditi, Lambling, and Cachera have devised a method of isolating the virus from ulcerative proctitis by inserting a portion of tissue under the skin of a guinea-pig. After a few days, the inguinal gland is excised, emulsified and injected intracerebrally into a monkey. In inoculated mice, a characteristic train of symptoms are evolved in five to seventy days, in which weakness, paresis, opisthotonos and convulsions occur, but the concentration of the virus in the injected mouse brain is not great, so that dilutions greater than 1 : 1,000 fail to give positive results.

A protection test has now been devised, by means of mixing equal parts of serum of the lymphogranuloma patient with an emulsion of mouse brain, diluted 1 : 5 in normal saline, and kept for the night in the ice-chest at 4° C.: doses of 0·5 c.c. injected intracerebrally do not

produce infection. The serum of monkeys which have recovered gives the same reaction.

Pathology.—The essential features of the pathology of the human gland consists in little pin-point epithelioid formations scattered all through the gland substance. They are made up of masses of irregularly disposed macrophage cells together with some giant cells. Höppli has described localized collections of eosinophiles. Subsequently tiny micro-abscesses form.

Primary sore.—Durand in 1913, and subsequently Hanschell, have described a small herpetiform ulcer on the prepuce which heals up in a few days, and the adenitis proper does not commence until after the primary lesion has healed. Hanschell does not believe that the disease usually occurs in the circumcised. The primary lesion is an erosion with clean edges, and is surrounded by a reddened zone, but with only slight infiltration and induration. The base of the ulcer is usually whitish-grey in colour.

It was formerly believed that the disease was unknown in women (Hanschell, 1926). It is now becoming recognized that typical inguinal poradenitis does occur in this sex, though inguinal bubonic manifestations are, on account of the different anatomical disposition of the lymphatic system in the female, comparatively rare; nevertheless, D. Galloway (1926) has recorded his familiarity with typical inguinal buboes in Chinese and Japanese prostitutes in Singapore. Most of the cases of inguinal buboes in women which have given a positive intradermal test (*see* below) have been reported by French writers in prostitutes, though definite evidence of the infection of a wife by her husband has been traced in an English case under the Editor's care.

Connection between climatic bubo, esthiomène, stricture of the rectum, etc.—When writing of the accompaniments of this peculiar infection the Editor feels that he is on less secure ground. Esthiomène has been recorded in all the countries of Europe and America, but there are very few references to its occurrence in native races, though Chesterman on the Congo has found typical cases amongst the native women, and also the genito-ano-rectal syndrome. Esthiomène is a condition of ulceration of the vulva associated with elephantiasis of the labia, which was formerly thought to be tubercular in origin. Stannus now believes, from a study of the literature, that esthiomène is the counterpart of climatic bubo in the male.

Gray and Yieh from Shanghai have described four cases in Chinese females. The primary lesion was probably hidden in the posterior wall of the vagina and the ano-rectal lymphatic gland is the first to be attacked. The infiltration of this gland extends, *via* the lymph-flow, to the anterior part of the vulva, and posteriorly to the rectum, resulting in the *genito-ano-rectal syndrome*, and finally scarring of the gland leads to rectal stricture.

Non-malignant fibrous stricture of the rectum, as found in both sexes, is probably due to the same virus. Authorities are now agreed

that syphilitic infection cannot be held responsible for this. However, rectal strictures would appear to be more frequent in Europeans than in native races, though Maxwell reports its comparative frequency in China; Gray has recorded it in both sexes in Nigeria, and Chesterman on the Congo. The relationship between this stricture and climatic bubo is not easy to prove, though in the Editor's opinion they are of the same ætiology. Recently he had a case of rectal stricture, 5 cm. from the anus, with ulceration of seventeen years' duration, which commenced with the breaking down of bilateral climatic buboes. A positive intradermal test was obtained. Rajam, in Madras, in a clinical study of climatic bubo and allied conditions, reviewed 183 cases of poradenitis, and found climatic bubo in 99 males and 2 females, and the genito-anal syndrome in 18 males and 8 females.

In 1932 Frei reported that 80 per cent. of cases of the genito-ano-rectal syndrome have given a positive intradermal test (Stannus, "A Sixth Venereal Disease," 1933).

Extra-genital infections have been recorded on the tongue, followed by glandular enlargements in the neck, by Curth; in the axilla by Hellerström; and on the foot by Lépinay and Grévin.

Symptoms.—The incubation period is three to four weeks after coitus, but it may be as long as six weeks to two months. The disease generally commences with pyrexia of a remittent type, which may precede the actual localizing signs and which may be mistaken for typhoid. Soon subacute inflammatory swellings of the groin glands may be noted. The inflammation may be unilateral or bilateral, while the oblique glands are most frequently affected, but at times it is the crural glands that are attacked. Sometimes one groin is affected after the other. In well-marked cases, the internal iliac glands can be felt to be enlarged and tender on deep palpation and sometimes the lumbar glands also. The signs of intoxication from absorption may be widespread and the Editor has treated many cases in lascars with high pyrexia and who appeared to be very ill. The affected glands slowly, or more rapidly, enlarge to the size of a hen's egg, or even larger and after several weeks, it may be months, the swelling gradually subsides. (Fig. 88.) Usually, the periglandular connective tissues inflame and the integuments become adherent till suppuration ceases. At other times fistulous tracks form, which continuously exude a clear sticky serous fluid. The most striking clinical feature in the male is the extensive inflammation of the periglandular tissues with comparatively little pain and comparatively small amount of suppuration.

It the suppurating glands be freely excised, the parts readily heal, but if they are left alone, or inefficiently treated, fistulous tracks develop which may take a very long time to heal. Sometimes also, if too much lymphatic tissue is removed, an elephantoid condition of the leg and scrotum on the affected side may develop (Fig. 89). This is a grave objection to surgical interference, added to the fact that secondary sepsis is very liable to ensue.

Sometimes, as the Editor has noted, rheumatic-like and painful effusions in the larger joints may accompany the pyrexial stages of climatic bubo.

Rupture of an extensive lymphogranulomatous suppuration into the urinary bladder has been described by Knabe.

Diagnosis.—The diagnosis of climatic bubo and lymphogranuloma inguinale has been placed upon a scientific basis by the introduction of the intracuti-reaction (intradermal test) of Frei (1925), which is now known as the Frei-Hoffmann reaction. The antigen is prepared from the inflamed gland tissue, though originally Frei used a heated saline dilution of pus aspirated from a softened inguinal bubo as antigen.

Fig. 88. Fully developed climatic bubo in right groin, showing also small primary lesion on the corona penis. (*A. H. Walters.*)

Frei's method of preparing antigen for the skin test consists of withdrawing the pus from a gland which has undergone softening, but not fistulation. The aspirated pus is mixed with physiological saline in the proportion of one part to five parts in a sterile tube, and immediately put up in ½-c.c. to 1-c.c. doses in Jena hard glass ampoules. Thus prepared, it is heated to 60° C. for two hours over a water bath, and the following day at 60° C. for one hour. The antigen should be preserved at a low temperature unexposed to light. Tests must be repeated every three months and should give negative reactions in skin of normal and control patients suffering from *ulcus molle.*[1]

A. H. Walters has modified the preparation of the antigen for routine use as follows:

An affected gland, surgically removed, is placed in a sterile glass dish. It is then cut in half and the two equal portions are placed in sterile Petri dishes marked 1 and 2. In specimen No. 1 the inner pin-point of necrotic material is macerated in physiological saline and inoculated at once into

[1] Careful experiments are now being conducted at the Albert Dock Hospital, London, with a controlled antigen prepared as above, and the results have been most satisfactory.

the inguinal region of guinea-pigs. Specimen No. 2 is macerated in physiological saline in dilution of 1 : 10 by weight and then macerated in a water bath at 60° C. for one hour; it is then filtered under strict aseptic precautions through fine Whatman paper in order to remove large masses.

On receipt of positive animal inoculation results, three batches of antigen are pooled and subjected to further inactivation at 60° C. for one hour on each of two consecutive days.

The test itself is carried out on the same lines as the Dick or Schick sensitization tests. 0·1 c.c. antigen is administered intracutaneously in the forearm, causing a wheal 8–10 mm. in diameter to develop. Physiological saline or *Dmelcos* chancroid antigen is administered on the other forearm as control. A positive result usually appears at the end of 24–48 hours and may vary in size from a circle of 1¼ in. in diameter to a considerable reaction about 3 in. in diameter. German writers have noted a hard mass ("*Ein harter Knochen*") of infiltrated skin which may persist for a few days. This never occurs in negative cases. The Wassén test consists of producing a fatal encephalitis in mice with inoculation of the virus.

The disease must be differentiated from venereal bubo, filarial adenitis, and plague, especially the ambulant form. In Hong Kong, for instance, especially amongst the military forces, climatic bubo has frequently and very charitably been known by practitioners as *pestis minor*. Climatic bubo may have to be differentiated from femoral hernia, and the Editor has seen both conditions associated together in Scarpa's triangle.

Blood changes.—There is usually a leucocytosis accompanying the suppuration. In the Editor's cases this has invariably been so; the leucocyte counts vary from 8,000 to 27,000 without any particular cell being affected.

Treatment.—In the lymphogranulomatous stage the inflamed gland, if discrete, can be excised, and this has been performed in the Editor's cases with conspicuous success by McIndoe, and undoubtedly the spread of further mischief appears to be avoided in this way, but surgical interference with the object of laying open the suppurating sinus or of removing large masses of lymphatic tissue should be strongly deprecated. As a result of this procedure the gland tissue may become secondarily infected with pyogenic organisms, a permanent lymphatic sinus may form, or a chronic lymphatic obstruction may ensue. Usually, excision of the mass when suppuration is present is not followed by clean and rapid healing, but by the reverse and the formation of more sinuses (Fig. 89).

During the acute stage of the disease, treatment should consist of rest and the application of soothing dressings.

Protein-shock therapy, according to Hanschell, is often followed by dramatic results, and the Editor has had considerable experience of this method of treatment. It is especially advantageous when suppuration has commenced, and should be combined with *aseptic aspiration* of the gland. This aspiration may have to be repeated on several occasions.

In giving protein shock, typhoid-paratyphoid vaccine (T.A.B.), or "Pyrifer"[1] is employed, commencing with 50 million given by the intravenous route and gradually increasing to 200 or 300 million, injections being given every third day. Two or three reactions are usually required till the buboes dry up and the surrounding induration disappears. This treatment should be combined with rest in bed, and antiphlogistine dressings. When there is active suppuration, eusol dressings and irrigations are best. In the chronic stage the Editor finds that applications of *ung. hydrarg.* promote healing.

Vaccine therapy.—The vaccine is prepared by excising a convenient portion of the gland mass, which is cut up into small pieces, dehydrated over calcium chloride, emulsified in saline and injected in increasing doses

Fig. 89.—Climatic bubo two months after incision and circumcision, showing sinus formation. (*H. Wolfe Cowen.*)

every second day, but no reliable results have so far been obtained by this method.

Tartar emetic.—Intravenous injections of tartar emetic have been used since 1925. Eight to fifteen injections of from 5 to 10 c.c. of a 1-per-cent. solution are required. The pentavalent compounds of antimony—stibenyl and stibosan in recognized doses—have also been employed with apparent success. Some authorities claim results with therapeutic application of X-rays.

Solganal B, in doses of 0·1–0·4 grm. given intramuscularly or intravenously, has been employed extensively and recommended in Germany. The Editor, however, has had little success with this method. Löhe and Rosenfeld (1932) use an oily suspension—2 per cent. for smaller doses, 20 per cent. for larger—in doses of 0·2 grm., increasing to 0·6 grm. intramuscularly, twice a week for a total of twenty injections (1·5 grm.).

Sulphanilamides.—MacCallum and Findlay, by means of chemotherapeutic

[1] Pyrifer is a B. coli preparation in strengths from 50–500 million, prepared by Aristopharm Ltd., Switzerland.

experiments on the virus of lymphogranuloma in the mouse, have shown that sulphanilamides have a definite value. Both with sulphanilamides and with a glucose derivative of 4 : 4 diaminodiphenyl sulphone, a considerable proportion of treated mice were saved. At present it is impossible to say why the virus of lymphogranuloma inguinale alone is susceptible to chemotherapeutic action, while so many other viruses are insusceptible, but the evidence so far obtained seems to point to the fact that living virus may still be obtained from the brains of certain mice after prolonged treatment with sulphanilamides.

In the treatment of the disease in man Rouie (1937) in Indo-China found the French preparation, rubiazol, curative, if given in courses over a prolonged period. Earle (1939) has reported on the value of M. & B. 693 (*sulphapyridine*) in 1·5 grm. daily, whilst C. N. Morgan has recorded a case which was cured with prontosil album.

Treatment of rectal stricture.—The treatment of rectal stricture due to this virus is difficult. Palliative measures consist in dilating the stricture by graduated bougies and injecting antiseptic solutions to cure the ulceration. Operative measures depend entirely upon the type of stricture present ; Lockhart-Mummery gives the following alternatives : Internal proctotomy ; complete proctotomy ; excision of the stricture or of the rectum ; and colostomy. Bensaude and Lambling, on the other hand, consider diathermic dilatation to be the best method of treatment, applied for twenty minutes every two or three days, for ten to twelve applications. Oil-soluble local anæsthetics, such as proctocaine, are the best for post-operative rectal pain.

The medical treatment of rectal stricture and esthiomène has been improved by the introduction of sulphanilamides. Shropshear claims success with these drugs, in doses of 2 grm. daily, for fifteen days, with a seven- to ten-day interval, when the course is repeated. Two patients required 108 grm. in two fifteen-day treatments before symptoms disappeared. C. N. Morgan (1939) finds that prontosil album, 1·5 grm. daily, in courses of fourteen days, and repeated after an interval of two months, resulted in cessation of the rectal discharge and in the healing of the rectal ulceration. In women, it checks the leucorrhœa and heals the ulcers.

CHAPTER XXXVIII

ULCERATING GRANULOMA OF THE PUDENDA

Synonym.—Granuloma Venereum.

Definition.—An infective and granulomatous condition of the pudenda, widespread in some parts of the tropics, conveyed by sexual contact and auto-inoculation.

Geographical distribution.—Ulcerating granuloma is widely diffused in India, Guiana, Brazil, West Indies, Porto Rico, Papua, Pacific islands, and Northern Australia; sporadically it occurs in the Southern United States, on the West Coast of Africa, and in Southern China. De Vogel relates that in the southern region of Dutch New Guinea this disease occurs in epidemic form and threatens the extinction of the local tribes. In only a single case was spontaneous cure observed.

Ætiology.—There is good reason for believing that the disease is generally, though not invariably, a venereal one; very rarely have extragenital lesions been observed. Cleland and Strangman in Australia, Flu in Surinam, and Aragâo in Brazil have described certain parasitic bodies within the large mononuclear cells from scrapings of the lesions. The organism is like a short bacillus with rounded ends, and measures 1 μ by 0·2 μ; it was described and named *Calymmatobacterium granulomatis* by Donovan, and later by Araujo. Later this organism was restudied by E. L. Walker, who considered it to be a capsulated intracellular diplococcus, probably *Bacillus mucosus capsulatus*, one of the Friedländer group. More probably, however, the secondary invader is the non-hæmolytic anaërobic streptococcus described by Meleney (p. 671).

Age and sex.—Ulcerating granuloma has not been recorded as occurring before puberty; it has been found only after the age of 13 or 14, and up to 40 or 50. It occurs in both sexes, but more often in women, especially where polyandry is practised.

Pathology.—Histologically this disease is allied to rhinoscleroma and the close association between these two diseases in Sumatra has been emphasized by Snijders. On microscopical examination the new growth at the margins of the sores is found to be made up of nodules, or masses of nodules, consisting of round cells having large and, usually, badly-staining nuclei. These cell-nests of Malpighian cells are embedded in a delicate fibrous reticulum. An important feature in the histopathology is a peculiar pathognomonic cell described by Pund and Greenblatt (Fig. 90). It is a large mononuclear varying from 25 to 90 μ in diameter probably derived from a plasma cell. The specific cell laden with the so-called Donovan bodies, can

be shown best by the *Dieterle silver impregnation* method in which these bodies appear as dark brown or black elongated ovoid masses with intense bipolar staining. The nodular masses are, for the most part, covered by epithelium, their under-surfaces merging gradually into a thick, dense, fibrous stroma in which small clusters of similar round cells are here and there embedded. The growths, though very vascular, contain no hæmorrhages; and there are no signs or suppuration or of caseation, no giant cells, and no

Fig. 90. Ulcerating granuloma of pudenda showing the pathognomonic cell.
After Pund and Greenblatt, "Archives of Pathology."

tubercle bacilli. In vertical section of the small nodules the round-cell mass will be found to be wedge-shaped, the base of the wedge being towards the surface; the deep-lying apex is usually pierced by a hair or two. The growth is found around sebaceous follicles, blood-vessels, lymphatics, and sudoriferous glands; but it is especially abundant, and most deeply situated, around the hair follicles.

Symptoms.—The incubation period appears to be a comparatively short one, from two to eight days after sexual contact, but it may be as long as twelve weeks. The disease commences in the great majority of cases somewhere on the genitals, usually on the penis or labia minora, or on the groin, as an insignificant, circumscribed, nodular thickening and elevation of the skin. The affected area,

which on the whole is elevated above the surrounding healthy skin, and covered with a very delicate, pinkish, easily-rubbed-off epithelium, excoriates readily, exposing a surface prone to bleed and break down, although rarely ulcerating deeply. The disease advances in two ways: by continuous eccentric peripheral extension, and by auto-infection of an opposing surface. It exhibits a distinct predilection for warm and moist surfaces, particularly the folds between the scrotum and thighs, the labia, and the flexures of the thighs (Fig. 91). Its extension is very slow, years elapsing before it covers a large area. Concurrently with peripheral extension, a dense, contracting, uneven, readily breaking-down scar forms on the surface travelled over by the coarsely or finely nodulated elevated new growth which constitutes the peripheral part of the diseased area. Occasionally islands of active disease spring up in this scar tissue; but it is at the margin of the implicated patch that the special features of the affection are best observed. In cases of long standing the partially-healed areas are covered with thin depigmented skin and thus show up as white patches.

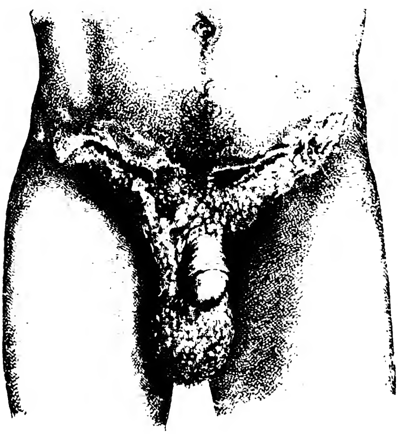


Fig. 91.—Ulcerating granuloma of pudenda in male.

In the case of the female (Fig. 92), the disease primarily attacks the crura of the clitoris, thence extending into the vagina, over the labia, and along the flexures of the thighs. The women thus affected are rendered sterile. In the male the disease may spread over the penis, involve the glans, scrotum, and upper part of the thighs. (Fig. 93.) Occasionally the glans penis is not involved. In either sex it may spread in the course of years to the pubes, over the perineum, and into the rectum, the recto-vaginal septum in the female ultimately breaking down. At times a profuse watery discharge exudes and even drips from the surface of the new growth, soiling the clothes, soddening the skin, and emitting a peculiarly offensive odour. In this condition the disease, slowly extending, continues for years, giving rise to inconvenience, and perhaps seriously implicating the urethra, vagina, or anus, but not otherwise materially impairing the health. In neither sex do the lymphatic glands become affected. The disease continues entirely local, but in the process of cicatrization the lymph-channels may become blocked, and pseudo-elephantiasis of the genitalia may occur. Impassable strictures of the

urethra may result, and recto-vaginal fistulæ are common. It may cause death by eating its way into the bladder and causing septic cystitis, as in a long-standing case under the Editor's care.

Diagnosis—Malignant and syphilitic ulcerations of the groin are common enough ; the disease under notice, however, differs widely from these—clinically, histologically, and therapeutically. It is characterized by extreme chronicity—ten or more years ; by absence of cachexia or of any tendency to cause death ; by non-implication of the lymphatic system as a whole, and by non-amenability to mercury and iodide of potassium.

The disease which it most resembles is lupus vulgaris. From this it differs inasmuch as it is practically confined to the pudendal region ; tends to follow in its extension the folds of the skin ; is not associated with the tubercle bacillus, giant cells, caseation, or other evidences of tuberculous disease.

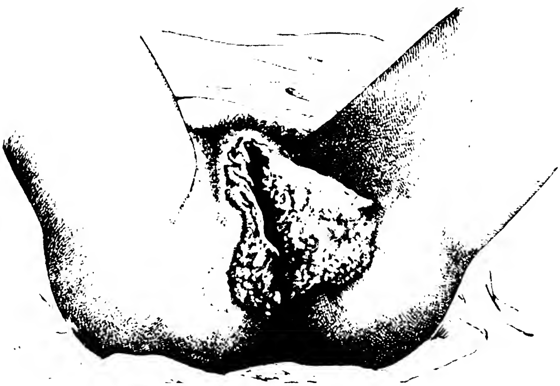


Fig. 92. Ulcerating granuloma of pudenda in female.

Unless complicated with a coincident syphilitic infection, which of course it may be, the Wassermann reaction is negative. The inefficiency of anti-syphilitic treatment soon convinces the physician that the ulceration is not due to this disease. Its characteristic mode of spread suffices to distinguish it from epithelioma and carcinoma. The discharges from ulcerating granuloma bear, moreover, a peculiar acrid smell. Pund and Greenblatt have described a fungating form affecting the cervix uteri in negresses, which greatly resembles the ulcerative and vegetative type of carcinoma of the cervix. It has also to be distinguished from gonorrhœal endocervitis and from simple erosion.

Treatment.—Scraping and caustics, including the actual cautery, have been freely employed ; but, although some improvement may be effected by these means, new nodules almost invariably spring up in the resulting cicatrix. Until recently complete excision, where practicable, offered the best chance of permanent cure ; such a proceeding had to be undertaken before large areas and important passages had become involved.

Judging from its relatively superficial nature and close resemblance to lupus, it seemed probable that ulcerating granuloma might prove amenable to some form of radiotherapy. This is actually the case, and X-rays, originally suggested by Sequeira and Macleod, have been successfully employed in Madras, though in some cases they appear to exert no effect whatsoever. Treatment by intravenous injections of tartar emetic, introduced by Aragão and Vianna in 1913, has also proved remarkably successful; improvement usually sets in, and, although in a small proportion of cases relapses occur, in the vast majority the cure is radical. The drug should be giv n as in kala-azar (*see* p. 195), but the amount requisite to effect a cure varies within wide limits. The Editor has had one case with a limited suprapubic lesion which healed completely after a total of 17½ gr. of antimony tartrate had been given altogether, while other cases require 170 gr. or more. Cicatrization usually takes place rapidly, but indolent ulceration may persist. Apparently stibacetin, stibosan, stibenyl, and other pentavalent compounds of antimony are more efficacious than tartar emetic. From 3 to 4 grm. of the drug are necessary in order to promote a cure. Giglioli in British Guiana gave two courses of seven intravenous injections with 45 days between each course. Each injection consisted of 0·1–0·6 grm. of stibenyl (stibacetin) dissolved in 20 c.c. of normal saline. He has produced cures by these means in cases resistant to tartar emetic. The Editor found it advisable to dress the open granulations daily with an ointment containing 1 per cent.[1] of antimony tartrate in white vaseline. It should be left on the sore for two hours, then wiped off carefully, and the sore washed with boracic solution and dressed with boracic ointment. Intermittent dressing with eusol helps to keep the surface clean. Radiant heat applied to the ulceration has proved

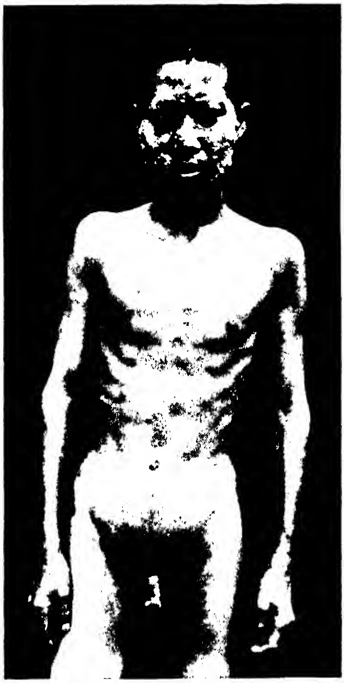


Fig. 93.—**Ulcerating granuloma of face and penis in a Chinaman.** (*Dr. B. Hawes.*)

[1] To make antimony-tartrate ointment, the necessary amount of antimony tartrate is first dissolved in a small quantity of liquid paraffin and then made up to strength with white vaseline. The ointment must not be spread on the healthy skin.

beneficial, while touching indolent spots with a silver-nitrate stick will sometimes promote healing. When the sore is of limited extent, excision and subsequent skin-grafting may be advisable, but a wide margin of healthy skin should be removed, or recurrence will most certainly take place. Tartar-emetic treatment may be combined with X-rays and with "protein-shock" treatment (Hanschell). These shock treatments should alternate with tartar emetic injections.

Fig. 94.—Ulcerating granuloma of the pudenda infected with non-hæmolytic streptococcus. (*Dr. Butterfield.*)
To show healing with zinc peroxide treatment and extensive scar-tissue formation.

Operative measures, such as the amputation of a badly ulcerated glans penis, may become necessary.

Combined with medicinal means, it is often necessary to open up sinuses and to cauterize undermined margins by means of the electric cautery.

Many observers have drawn attention to types of ulcerating granuloma which are unaffected by antimony. F. L. Meleney has emphasized the curative action of *zinc peroxide* in the treatment of anaërobic and certain acute surgical infections. It has been used since 1903 by French and German surgeons, but for many years fell into disuse. Now it has been taken up anew by Meleney in chronic ulcerations due to non-hæmolytic anaërobic streptococcal infections which have hitherto resisted all other forms of treatment ; it is to this

category that the ulceration of ulcerating granuloma belongs. The standard preparation of zinc peroxide is one which, when sterilized and suspended in distilled water, consistently yields oxygen while itself remaining of a soft consistency. In its application it is necessary that it should be rubbed into the wound, especially at its spreading margins, in gangrenous infections of the skin due to synergistic bacterial action, and in undermining burrowing ulcers of the non-gangrenous type.

The liberation of oxygen depends upon the presence of water, and therefore zinc peroxide cannot be employed in oily solutions. The best preparation is from the Du Pont Chemical Co., Niagara Falls. It is necessary to sterilize it at 140° C. for four minutes; 5–25 grm. are put up in large test-tubes, the contents of which are mixed, by means of a syringe, with enough distilled water to give a homogeneous suspension with the consistency of 40 per cent. cream; this is spread so as to come into contact with every part of the infected surface, particular care being taken to see that it gets under the undermined skin and down into the sinuses, for which it is frequently necessary to use a short catheter. Strips of gauze or silk are dipped into the suspension, and introduced into the sinuses. The dressings should be changed daily, but in painful cases the dressings may be left for two days to commence with. The Editor has seen one very extensive case successfully treated in this manner when all other measures had failed (Fig. 94). It was found advantageous to syringe out the sinuses with hydrogen peroxide in addition. All sinuses must be thoroughly opened up by surgical means.

Probably the verification of this streptococcal infection explains the enthusiasm now being shown for *sulphanilamide therapy.* Ross has recorded the striking action of M. & B. 693—six tablets of 7·5 grm. (i.e., 3 grm. daily) for fourteen days—in limited ulcerating granuloma lesions.

Prophylaxis.—As this disease is most certainly spread by sexual connection, prevention consists in the avoidance of illicit intercourse, especially with native women.

Section VII.—TROPICAL SKIN DISEASES

CHAPTER XXXIX

NON-SPECIFIC, BACTERIAL, AND FUNGOUS SKIN DISEASES, ETC.

I. NON-SPECIFIC SKIN DISEASES

Leucoderma

Leucoderma, or vitiligo, is extremely common throughout the tropics, and is by no means confined to any particular race. Almost any part of the body may be affected. The atrophied, unpigmented

Fig. 95.—Leucoderma. (*Dr. H. K. Griffin.*)

patches of skin slowly enlarge in a peripheral direction, and may coalesce. Occasionally the whole body is affected, and a certain amount of symmetry may be observed ; the hair of the affected parts may also become white (Fig. 95). The texture and glands of the skin remain normal. The ætiology of the disease is unknown, but it is

thought to be a tropho-neurosis. No treatment is of any avail. It is possible that those cases with a positive Wassermann reaction are syphilitic in origin and may be benefited by antisyphilitic treatment. Care must be taken not to mistake this condition for the depigmentation which is commonly seen in macular leprosy.

Cheloid

Synonym.—Keloid.

The term cheloid is applied to an overgrowth of fibrous tissue in the cellular layers of the corium. Hypertrophic scars are common enough in Europeans consequent upon surgical scars or burns, but there are those who are predisposed to develop the extensive hyperplasia which is known as cheloid. Central African negroes are especially liable, and in some tribes cheloidal scars on the back, thighs, or chest constitute a readily recognizable tribal mark. Similar fibrosis may occur in these people consequent upon a cautery, or marking the site of a healed syphilitic chancre, or even mosquito-bites.

When fully developed, the growth is well defined; on a white skin it is pinkish or brownish in colour, but has a distinct red or chocolate tinge on a dark person. Growth takes place very slowly and, rarely, sarcomatous changes may supervene in the fibrous tissue. The growth may cause intense pain when forming, or give rise to a continuous ache.

Treatment.—The most efficacious method, according to Macleod, is by radium. A full-strength radium plate is used, and is screened off by a silver sheet 1 mm. in thickness. The exposure should be one of 18–30 hours. Less brilliant results are obtained by means of CO_2 snow, especially in early lesions. Electrolysis (3 ma.) is also useful, while occasionally X-rays are satisfactory.

II. BACTERIAL SKIN DISEASES

Tropical Sloughing Phagedæna

Synonym.—Ulcus Tropicum.

Geographical distribution.—Sloughing phagedæna is common in most tropical countries, particularly in those with a hot, damp climate, principally in the jungle. These sores are often named after the regions in which they are specially prevalent—Mozambique ulcer, Yemen ulcer, Naga sore (Assam), etc.

Occasionally this disease assumes epidemic proportions. Thus, Lloyd Patterson described one such epidemic which "swept like a plague up the whole of Assam," seriously interfering with the efficiency of the labour force on the tea plantations.

This form of phagedænic ulcer was very common among the carriers attached to the East African Force during the Great War, and accounted

for a considerable amount of invaliding, and its prevalence in Kenya among natives causes an immense amount of disability.

Tropical ulcer is the commonest cause of disability amongst labourers in Malaya. The average stay in hospital is 141 days in younger patients and up to 232 days in older ones, so intractable are these ulcers to treatment. This ulcer is also a terrible scourge in the Solomon Islands, New Guinea, and indeed in the whole of Melanesia.

Ætiology.—Prowazek attributed these ulcers to *Spirochæta schaudinni*.

Although sloughing phagedæna is evidently a germ disease, it is not readily communicated by ordinary inoculation either to man or to the lower animals. Apparently a concurrence of certain unknown conditions is essential. Lloyd Patterson, however, by bandaging a swab smeared with discharge from a typical sore on to the surface of an abrasion from which the scab had been removed, succeeded in producing a characteristic sore.

Sloughing phagedæna is apt to attack the half-starved, malaria-stricken pioneers in jungle lands, over-driven slave gangs, and soldiers campaigning in the tropics. In such circumstances a slight wound, an abrasion, even an insect-bite, or an old chronic ulcer may serve as the starting-point for one of these terrible sores. Where yaws and sloughing phagedæna are coendemic, the sores of the former may become infected with the virus of the latter, and serious sloughing and cicatricial contractions result. The feet and legs, being most exposed to injury, are the most frequent locations of this form of ulceration; but the arms, or any other part of the body, may also be attacked. The blood-calcium content, blood-sugar and blood-urea are said to be much diminished, probably as the result of deficient dietary (McCulloch). On the other hand, the Editor has treated several severe cases in otherwise healthy and well-fed Europeans in whom a dietetic deficiency could hardly be seriously considered.

Clements in Melanesia and James in the Solomon Islands are strongly of the opinion that diet deficiencies (especially B_2), debility and climatic factors combine in predisposing to ulcus tropicum. For instance, the incidence in sago-eaters is vastly greater than those who subsist on taro. They consider that fusiform bacilli and spirochætes play a considerable part in tissue-destruction. A close relationship with chronic malaria appears to be possible in the epidemic form of this disease, and stress is laid upon the importance of Buxton's line of separation between the malarial and non-malarial Pacific islands, which also marks the separation between phagadænic islands, and those ulcer-free. It is apparently true that the virulence of the organisms responsible for ulcus tropicum is increased by transmission amongst susceptible people.

Symptoms.—If the disease occurs in previously sound skin, the first indication is the formation of a larger or smaller bleb with sero-sanguinolent contents. The formation of this may be attended with

some pain and constitutional disturbance. When, in the course of a few hours, the bulla ruptures, an ash-grey, moist slough is exposed. The sloughing process rapidly extends in all directions until the skin and subcutaneous fascia over an area of an inch to many inches in diameter are converted into a yellowish, moist, horribly stinking slough. After a few days the centre of the slough begins to liquefy, the sore still continuing to extend at the periphery. In the course of a week or longer the sloughing process may cease and the slough be gradually thrown off. (Fig. 96.) Then it is seen that, not only have the skin and superficial fascia been destroyed, but in bad cases possibly muscles, tendons, nerves, vessels, and even the periosteum of the bones, have

Fig. 96.—Ulcustropicum. (*Editor's case.*)

shared in the gangrenous process. Fortunately, in many instances, the deeper structures are spared, the disease being relatively limited and superficial. Sometimes, however, important structures, including joints, bones, and large blood-vessels, are destroyed : in such cases, even if life be spared, great deformity may ensue from different forms of ankylosis, or from strangulation of a distal part by a contracting cicatrix, necessitating amputation (Fig. 97).

Diagnosis has to be made from the ulceration of yaws, syphilis, amœbic ulceration of the skin, oriental sore, varicose ulcers, and veld sore, and is usually not very difficult, a final diagnosis being arrived at by process of exclusion.

Treatment.—As recent observations in Kenya Colony and Tanganyika Territory have shown that dietetics play an important part in the production of ulcus tropicum, it is of the first importance to

endeavour to correct any cachectic state which may be present. Thus good food, fresh vegetables, lime-juice, and quinine are almost invariably indicated. Corkhill in the Sudan finds that much the same conditions hold there: cod-liver oil dressings, for instance, combined with a liberal vitamin A dietary give good results. Opium in full doses, not merely to assuage pain, but on account of its special action on the phagedænic process, is usually of great service.

If the sore is extensive and septic, the patient should be anæsthet-

Fig. 97.—Ulcus tropicum: acute case in a European, eventually causing loss of leg. (*Editor's case.*)

ized, and the surface properly scraped and subsequently swabbed with pure carbolic. Directly healthy granulations appear, the ulcer should be treated on general principles. Other authorities prefer strong commercial formalin applied lightly once a day for two or three days, followed by a bismuth paste (B.I.P.) directly a scab has formed.

James, in his hospital in New Britain, states that ulcers and their complications account for most of the deaths. In serious cases curetting or excision is often necessary, followed by skin

grafting, with or without *copper sulphate treatment.* James' method is as follows :

Copper sulphate	1 oz.
Glycerin	2 oz.
Acid carbolic, 1 drm. to oz. of resulting solution.	

After crushing the copper, it is placed with glycerin into an enamel bowl and heated. It is then stirred and allowed to cool and a drachm of carbolic is added to each ounce of solution. The ulcer is gently cleaned with wool swabs, the limb is placed horizontally, and the solution is applied on a piece of wool the size of a pea, the application being continued for two or three minutes. A dressing of acriflavine, 1 : 1,000 on gauze is applied and is covered by a hot fomentation. The application may have to be repeated twice daily. Most ulcers are clean after applications on two consecutive mornings and on the fourth morning scarlet-red ointment and adhesive plaster can be applied. A somewhat similar method is advocated by Acton and Panja.

Harley-Mason in Kenya emphasizes the value of tar as an application in the mass treatment of natives, and has reported upon 300 cases treated in this manner. The ulcer is first swabbed out with eusol, any sloughs present are removed, and the surrounding skin is cleaned. The tar is spread upon lint and changed every two or three days. Subsequently zinc ointment is used ; applications of zinc oxide and ichthyol are also recommended. Strocchi first cleanses with hydrogen peroxide and then applies gauze saturated with a preparation of arsenobenzol and iodine known as Neojodo I.C.I.

Small superficial ulcers respond readily to powdering with iodoform, or B.I.P. dressing, and subsequent firm strapping with elastoplast after Dickson Wright's method. When elastoplast cannot be obtained, a 3-in. spiral bandage acts well. Sayers in the Solomon Islands finds this method particularly suited to the natives of that region. The strapping must be left on for one week. The Editor has also had successes in intractable cases with this method in Europeans. This method is based on the principle that the best dressing for the ulcerated surface is its own discharge. Two longitudinal strips of elastoplast are applied to cover the malleoli and further longitudinal strips are placed over the instep, over the tendo Achillis, and over the ulcer itself. A circular bandage is then applied, commencing from the toes and winding spirally up the leg. No dressing is used. After twenty-four hours in a bad case pus leaks through the bandage and the smell becomes objectionable. Then a plain bandage is applied, and if the discharge is excessive the bandage is removed after three days. At this time the ulcer may be larger, but epithelization will be occurring at the edges, and healthy granulations will appear. Spraying with insulin has been found by the Editor to promote healing at this stage. The leg should then be restrapped and not touched again for a week.

Then there is another class of case where every simple method fails and the ulcer continues to spread in spite of the most energetic measures. In these cases total excision of the ulcer followed by Thiersch-grafting offers the only means of ultimate success. This method has been used by Brennan, Anderson, and Roberts in Kenya, and James in the Solomon Islands. By means of a large curved bistoury the whole of the infected tissue is removed. The ulcer is excised under spinal anæsthesia and not scraped. The resulting wound should be dressed with eusol and ointment twice daily till the surface is clean.[1] Afterwards a dressing of B.I.P. should be applied once daily for some days until it is certain that there is a granulating surface. The site is now treated by skin grafting. According to Enzer, when the Thiersch method fails, "pinch grafting" of small circular patches of whole skin distributed over the area should be employed. It is said that complete healing takes place in fourteen days. The Editor has had experience of two such cases in Europeans where grafting ultimately succeeded when all else had failed. The grafts should be dressed with an emollient ointment, *Tull Gras Lumière* (Anglo-French Drug Co., 238, Gray's Inn Road, W.C.1). Workers in Kenya agree that the grafts usually take readily, and the stay in hospital after operation is one of twelve to nineteen days.

In contrast to the energetic measures described above, Loewenthal in Uganda claims brilliant results with intravenous injections of calcium. Fifteen grains of calcium chloride in 10 c.c. of distilled water are injected intravenously daily till the cure is complete, and if a case proves resistant, the dose is doubled. It is said that the offensive odour is lost in the first week, sloughs in the second, and in the third there is a healthy granulating surface with rapidly extending epithelization. However, it is probable that, though disordered calcium metabolism may play some part in the production of these ulcers, yet the results of treatment would be improved by scraping and skin-grafting.

Kerby reports that zinc ionization is useful in healing up residual areas of ulceration. For this purpose a 1-per-cent. solution of zinc sulphate has been used at the rate of 2 ma. to the square inch for 20–30 minutes.

Veld Sore

Synonyms.—Septic Sore; Desert Sore; Barcoo Rot.

Geographical distribution.— This peculiar ulceration is widely distributed in the tropics and subtropics wherever desert conditions exist. It has long been known in Queensland and the Northern Territory of Australia. It affected the British troops in the Sudan and South African campaigns, and caused a very considerable amount of disability in Gallipoli, Egypt, Palestine and Iraq during the Great War. In South Africa it is familiar to sportsmen and travellers.

[1] Sayers finds that acriflavine 1 : 1000 with normal saline is the best solution to clean up a suppurating surface. It is applied on dry gauze and the wound surface is swabbed with normal saline before the bandage is applied.

Ætiology.—The cause of this condition has long been obscure. In 1916 Craig, working in the Sinai Desert, demonstrated the diphtheria bacillus in the lesions. Whether this covers the ætiology of all veld sores cannot at present be affirmed, but that a certain proportion are diphtherial in origin may be taken as established. By sterilizing the surface of the sore with absolute alcohol and scraping the clear surface, a pure culture of the Klebs-Löffler bacillus may be obtained on Löffler's serum. This organism is pathogenic to guinea-pigs and quails, and its lethal effects may be neutralized by injection of antidiphtheritic serum. In the serous contents of the blebs the typical granular bacillus may be observed in stained preparations. (Fig. 98.)

The desert sores, as the Editor observed them among British troops, occurred most frequently in men of mounted units, especially those associated with camels. The rate of incidence coincided with that of a widespread epidemic of faucial diphtheria.

Fig. 98.—Culture of Klebs-Löffler bacillus obtained from the veld sore shown in Fig. 99.
(*Dr. H. K. Griffin, Assiut, Egypt.*)

Symptoms.—The sores occur almost invariably on the exposed parts, mainly those covered by hairs, such as the dorsum of the hand, the fore-arm, the elbows and knee-joints. Sometimes the lesions occur on the face, over the eyebrows and on the cheeks. They may arise *de novo*, or be superimposed on some abrasion.

A regular sequel of events precedes the actual ulceration. At first a *vesicle* full of straw-coloured fluid makes its appearance, generally in the vicinity of a hair follicle; it may vary considerably in size. The pain it occasions is quite out of proportion to the size of the lesion. On bursting it leaves behind a shallow *ulcer* covered with a thin grey pellicle. The raw ulcerated surface is exquisitely tender, and it may continue to spread peripherally. (Fig. 99.)

After the inflammatory changes have lasted two or three weeks the ulcers enter upon a *chronic stage*. At this stage they are characteristic in appearance and perhaps are more familiar to tropical practitioners and medical officers than when in the incipient stages. The ulcers are punched-out, circular in outline, with undermined edges and thickened margins; their base is covered with grey-coloured and scaly debris, beneath which one can frequently distinguish an adherent membrane, but little or no pus is discharged. The peculiar ulceration which results is most intractable, and resists all external forms of medication; the edges become indurated, and the thickened tissue has a cyanotic appearance. In sores in which healing does take place a thin paper-like scar remains, and persists for several years. The actual ulceration may continue for two years or longer.

The Klebs-Löffler bacillus can be isolated with ease only from the primary lesions; from the chronic ulcerations it is recovered with difficulty, being overgrown with staphylococci and other organisms of suppuration.

Typical diphtheritic pareses, or paralyses, have been observed in association with these sores; in one series this complication occurred in 27 per cent. Paralysis of the palate, arms, and legs, and accommodation paralysis of the iris, have been observed. There may be ataxia, loss of knee-jerks, anæsthesia, and incoordination, recalling at first sight locomotor ataxia or beriberi. Walshe has pointed out that the initial local paresis is in anatomical relation to the site of the infective focus.

Treatment.—The specific treatment for this kind of ulceration is antidiphtheritic serum, which has a very striking effect in healing up ulcers that have persisted for a year or even longer. At least 4000 units should be given, and should be injected subcutaneously in the vicinity of the sores. The sores

Fig. 99.—Veld sore on leg containing growth of Klebs-Löffler bacillus. (*Dr. H. K. Griffin.*)

themselves may be dressed with lint soaked in the same serum or with weak formalin.

Prophylaxis.—Protecting against abrasion exposed parts of the body, especially the knees, in desert regions where these sores occur, is obviously indicated. Mounted men should wear knee-breeches and should not be permitted to ride in shorts. The application of antiseptic lotions to any abraded surface at the earliest possible moment is also indicated. As there is some evidence that dried horse-manure may act as a nidus of the bacillus, care should be taken to avoid contact with this substance as far as possible.

Amœbic Ulceration of the Skin and Subcutaneous Tissues

A peculiarly destructive type of ulceration of the skin with involvement of the deeper tissues may occasionally occur in the vicinity of amœbic lesions caused by the invasion of the cutis by tissue-invading forms of *Entamœba histolytica*. This has been noted around discharging sinuses from a liver abscess on the chest-wall, or in the perineum in the vicinity of the anus. The skin in these regions affords a suitable

medium for the multiplication of the amœbæ, and the ulceration, once it has commenced, spreads with great rapidity (p. 563).

The differential diagnosis has to be made from ulcerating granuloma of the pudenda, from the gummatous ulceration of syphilis or yaws, from actinomycosis, from tubercular ulceration, and from massive gangrene of the skin, or the chronic infectious gangrene described by Meleney. The treatment of amœbic ulceration of the skin is very satisfactory, and it yields almost instantaneously to injections of emetine and other anti-amœbic drugs.

Boils

The anatomical and clinical features of this painful affection are too familiar to require detailed description. Suffice it to say that a boil is produced by the proliferation of *Staphylococcus pyogenes aureus* and *albus*, *Streptococcus pyogenes*, or other pyogenic micro-organisms, in the skin and subcutaneous tissue; that the organism gives rise to local and limited infiltration of the tissues with lymph, leading to necrosis, the central core being surrounded by an areola of acute inflammation; that this core is separated by a process of sloughing and so got rid of, the resulting ulcer speedily healing, and leaving a depressed scar which, when occurring about the legs, may become pigmented. Though a self-limiting disease locally, it is nevertheless capable of being inoculated elsewhere in the same individual, both through a breach of surface and also by simple contact of the discharges with the skin, the micro-organism apparently entering by a hair follicle. This auto-inoculability of boils is apt to be overlooked.

Conditions of debility, presumably by lowering resistance, predispose to boils; the subjects of diabetes are especially prone to them, the saccharine state of the blood or secretions seeming to be particularly favourable to growth of the specific germ. In the tropics, too, boils are the frequent accompaniment of and sequel to malaria.

Treatment.—Boils ought never, unless in very exceptional circumstances, to be poulticed. Poulticing, although it may relieve the pain of the existing boil, is prone to be followed by more boils in the area sodden by the heat and moisture. Neither should boils be incised, or squeezed. The only exception to the rule of not cutting is in the case of boils occurring in the scalp or in the axilla. In the former situation, unless opened early, they are apt, especially in young children, to burrow and cause troublesome abscesses; in the latter situation boils tend to be very indolent and painful, and do not readily break through the lax integuments.

In any situation in which the boil is liable to be irritated by pressure or clothing, it is sometimes a good plan to cover the part with a circle of wash-leather spread with soap plaster, and having a small hole cut in its centre corresponding to the apex of the boil, or under modern conditions with a specially-prepared elastoplast strip. When a boil opens, the discharge must

be kept from soiling the adjoining skin, and the patient must be warned against touching the skin elsewhere with pus-soiled fingers. The parts must be frequently cleansed with 1 : 1000 corrosive sublimate lotion, powdered with boric acid, and covered with a dry, absorbent antiseptic dressing. A threatening boil may often be aborted by touching the little initial itching or vesiculated papule with some penetrating antiseptic, as iodine tincture, or by painting it with collodion. A very successful method is to drill slowly into the centre of the papule with a pointed pencil of hard wood dipped in pure carbolic acid. The point of the pencil should penetrate at least an eighth of an inch, and should be frequently recharged with the acid during the drilling process; the pain is trifling. In this way, in a severe attack of furunculosis, boil after boil may be aborted and the attack brought to an end. In obstinate chronic furunculosis excellent results have occasionally attended treatment by injections of an autogenous vaccine commencing with a dose of fifty millions and working up to three hundred millions of organisms.

The effect of the sulphanilamides on pyogenic suppuration has to be noted. In Uleron (Bayer), given in full doses of 3 grm. per diem, we possess a specific for some cases of staphylococcal suppuration.

Pemphigus Contagiosus (Pyosis Mansoni)

Geographical distribution.—Pemphigus contagiosus is very common in South China during the hot weather; in some years it may even be described as epidemic. It is perennial in the Straits Settlements, and it is known in Ceylon, Madras, in North Queensland, Japan, and America. European children are more prone to it than native children; European adults are by no means exempt, but the native adult is rarely affected.

Ætiology and pathology.—Like impetigo contagiosa, this is undoubtedly a germ disease, caused by streptococci and staphylococci. Manson originally found a diplococcus in the epidermis and in the fluid of the blister.

Symptoms.—Pemphigus contagiosus closely resembles certain forms of the impetigo contagiosa of temperate countries, and is probably a variety of this class of skin disease. The individual lesions, as can readily be ascertained by inoculation experiments, begin as minute erythematous specks, which rapidly proceed to the formation of vesicles, bullæ, or even large pemphigus-like blisters.

Pemphigus contagiosus may occur in almost any part of the body. In young children it is usually diffuse; in adults it is mostly confined to the axillæ and crutch.

Diagnosis.—Absence of constitutional symptoms, or of a history of such, distinguishes pemphigus contagiosus from chickenpox. Absence of trichophyton elements and of a well-defined, slightly raised, festooned, and itching margin, together with the presence of large blebs and scaling of the epidermis, distinguishes it from ordinary forms of body ringworm—a disease with which, when occurring in the armpits and crutch in adults, it is frequently confounded.

Treatment.—Cleanliness, the frequent use of a corrosive sublimate lotion (1 : 1000) and a dusting-powder of equal parts of boric acid, starch, and zinc oxide, or ammoniated mercury ointment are specially effective. Undoubtedly sulphanilamide compounds, especially M & B 693 in full doses of 3 grm. daily to an adult, may be found useful. In the school and nursery those responsible for the care of children must be informed of the contagiousness of this unpleasant affection, and measures be instituted accordingly.

Craw-Craw and Ulcerating Dermatitis

Synonym.—Nodular Dermatitis.

Symptoms.—The term craw-craw is very loosely applied. Emily has described under this name a papulo-pustular skin affection which is common in certain parts of tropical Africa and is often the cause of much suffering to the traveller. It, or a similar disease, is by no means confined to Africa, for it is seen in patients from Ceylon and India, and Manson was at one time very familiar with it in South China. The disease begins as an itching papule, very possibly at the seat of a mosquito-bite. The itching provokes scratching, whereby some form of pyogenic micro-organism is inoculated. Pustulation follows, and is spread over feet and legs by soiled shoes and stockings, and auto-inoculation. In this way an ulcerating, pustulating dermatitis is kept up.

In the exudate of these papules O'Neil found small filaria embryos which resembled the embryo of *Acanthocheilonema perstans*. Brumpt does not believe that these are examples of the embryos of *Onchocerca volvulus*, as has been affirmed. Possibly they are the same as the microfilaria described by Macfie (*see* p. 965). It may be, too, that many of these cases are in effect an allergic manifestation of a systemic filarial infection by *L. loa* or *A. perstans*.

Diagnosis.—The hard, horny papules of craw-craw have to be differentiated from scabies, which is common in African natives. It has to be distinguished from the lichenoid eruptions caused by microfilaria volvulus (p. 963).

Treatment.—Emily describes a very efficient treatment. Pustules are opened, crusts removed, and ulcers scraped. Boric-acid powder is then dusted freely on the parts after a thorough scrubbing with sublimate lotion (1 : 1000); borated vaseline is applied on lint, and this is covered by absorbent cotton and a bandage. The dressings are not disturbed for a week, when the parts will be found soundly healed. Similar auto-infective diseases, so common in the tropics, may be treated by prolonged soaking in a warm carbolic-acid lotion (1 : 20), followed by dry dressing with boric powder. Infected slippers, shoes, and stockings should be destroyed.

Cercarial Dermatitis

Cort in Michigan (U.S.A.) in 1928 drew attention to a special kind of dermatitis produced by *Cercaria elvæ*, and soon after *C. douthitti* was found to cause similar lesions. In England and Wales dermatitis from bathing in ponds and reservoirs has been noted by Matheson, Taylor and Baylis as due to *C. ocellata*, a form closely allied to *C. elvæ*. The cercariæ burrow in the skin and their heads become arrested there and cause a pustu'ar eruption. All these cercariæ are derived from different species of *Lymnæa* especially *L. ocellata*. *C. elvæ* and *C. ocellata* are large cercariæ nearly 1 mm. in length overall, twice that of the bilharzia cercariæ; the tail is bifurcated and all possess two suckers. Cercarial dermatitis is commonly known as "sedge-pool itch" or "swimmer's itch," and takes the form of an itching maculo-urticarial dermatitis, later becoming papular or pustular; it may be, after a few days, actually exanthematous. It is always connected with paddling or swimming in infected waters a few days previously.

Pyrethrum Dermatitis

Pyrethrum dermatitis has been noted in Kenya, and is caused by the leaves and flowers of *Chrysanthemum cinerariæfolium*, which grows at altitudes

of 500–7000 feet and flowers throughout the year. The pyrethrum content is 1–2 per cent. Absorption is facilitated by constant sweating, and exposure to sunlight greatly exacerbates the lesions. Some persons on contact exhibit merely a local dermatitis ; in others it produces a widespread allergy. Itching commences at the corners of the eyes, and this is followed by lachrymation, an irritating vesicular rash, peeling of the skin, and the formation of painful fissures.

III. FUNGOUS SKIN DISEASES

Prickly Heat

Prickly heat, or, as it is sometimes called, lichen tropicus, is probably a form of miliaria (not of lichen) connected with the excessive sweating incident to the heat of tropical climates.

According to Pollitzer, the mechanism of its production depends on the non-cornification of the cells of the stratum corneum, the individual cells of which, in consequence of their being sodden by constant perspiration, swell, and so obstruct the orifices of the sweat-glands, thereby leading to accumulation of sweat in the ducts.

Ætiology.—In scales obtained from the lesions, E. C. Smith has been able to demonstrate yeast-like budding forms and branching mycelium of a species of Oidium.

Tubes of Sabouraud's medium are sown with three or four fragments of scales and maintained at room-temperature. Within six days the fungus appears as an opaque, creamy-white growth. Occasionally a variety is encountered which produces a red colour. In order to obtain it in pure culture, frequent subinoculations are necessary. Microscopically the pure cultures are composed almost entirely of budding forms, staining by Gram. Occasionally short mycelial filaments are encountered.

In scales these yeast-cells can be demonstrated by Gram's method.

Superficial application of cultures to the human skin reproduces the natural disease. A piece of lint 1 in. in diameter is moistened with a thick emulsion of a twenty-four-hour agar growth, applied to the shaved skin and maintained in close contact by adhesive plaster. The incubation period is about four days. The area is then found to be covered with minute sudaminal, or herpetic-like vesicles. In the scales collected from the surface of these vesicles the fungus can be demonstrated as well as in the superficial parts of the hair follicles.

The lesions are probably produced by two factors ; the mechanical factor is supplied by the irritation produced by a foreign body, the toxic by the fungus itself. This combination produces a progressive œdema of the cells in the vicinity. The portion of the hair follicle which passes through the epidermis is involved.

Nearly every European in the tropics suffers from prickly heat, particularly during the earlier years of residence. Some never seem to become acclimatized in this respect, but continue year after year to exhibit their crop of prickly-heat lesions when the hot season comes round.

Though sufficiently annoying in the robust and healthy, in them prickly heat is not a grave affair. It is otherwise in the case of the invalid, of delicate sickly children, of hysterical and, especially, of parturient women; to these it may prove, by interfering with sleep and provoking restlessness, a very serious matter. Prickly heat is also a common though indirect cause of boils; for the breaches of surface following on the scratching it induces afford many opportunities for invasion by the micro-organisms of furuncular disease.

Prickly heat consists of a miliary-like eruption, generally most profuse on those parts of the body, as around the waist, which are closely covered with clothing; but it also occurs on the backs of the hands, on the arms, legs, forehead, occasionally on the face, the scalp, in fact on any part of the surface of the body except the palms and soles. The minute, shining, glass-like vesicles, and the numerous, closely-set, slightly inflamed papules, give the skin the feeling as if thickly sprinkled with grains of sand. The eruption may keep out for months on end, becoming better or worse according to circumstances. The pricking and itching are often exceedingly distressing. Anything leading to perspiration immediately provokes an outburst of this almost intolerable itching—nothing more certainly than a cup of hot tea or a plate of hot soup. Long drinks, exposure to the hot sun, close rooms, warm clothing, all aggravate the distress. Sometimes the little vesicles pustulate, doubtless from micrococcus infection. As soon as the weather becomes cool the eruption and the irritation quickly subside.

Treatment.—Manifestly, the most important thing is the avoidance of all causes of perspiration particularly the copious consumption of fluids, especially hot fluids—moderation in exercise, avoiding sea-bathing, close rooms, warm clothing, and so forth. Soap should not be used in the bath. The sleeping-mattress and pillow should be covered with a finely woven grass mat, and the bed provided with what is known in the East as a "Dutch wife"—that is, a hollow cylinder, 4 ft. by 8 or 10 in., of open rattan work, over which the arms and legs can be thrown, and unnecessary apposition of sweating surfaces so avoided. A punkah at night is a great comfort. Afridol soap (Bayer), containing oxymercuriotoluylate of sodium, in which mercury is in non-ionizable form, can be recommended as a preventive and a curative measure in prickly heat. The soap is powerfully germicidal and should be used twice daily with warm water. A firm lather should be produced in warm water and applied to the affected parts. The lather should be left to dry on the skin for a quarter of an hour so that it can exercise its full effect, after which time it can be thoroughly washed off. When used as ordinary soap it acts as a preventive against prickly heat. Midgley's "Medisoaps" are also to be recommended, especially one containing 20-per-cent. carbolic acid, and another containing mercury biniodide. Every bathroom in the tropics should be provided with some mildly astringent and antiseptic dusting powder. A very good one consists of equal parts

of boric acid, oxide of zinc, and starch. This should be freely applied, after careful drying of the skin, particularly to the axillæ, the crutch, under the mammæ in women, and between the folds of skin in fat children and adults. A simple precaution of this sort saves much suffering both from prickly heat and from epiphytic skin disease. Ruge recommends rice powder containing a little *Desitin*.

The frequent application of a salicylic-acid (1 dr.) and spirit (8 oz.) lotion has been advised. Pearse strongly recommends the inunction of a mixture of almond oil and lanolin in the proportion of 8 to 1 and scented according to fancy. Some consider thin flannel a better wear than cotton or linen as a preventive of prickly heat. Sometimes the following powder, gently rubbed in for five or ten minutes with a damp sponge, will cure bad patches: Sublimed sulphur, 80 parts; magnesia, 15 parts; oxide of zinc, 5 parts. Calamine lotion, with or without hydrocyanic or carbolic acids (2 per cent.), relieves the itching and is strongly recommended.

Tropical Cheiropompholyx

This is a name given to vesicular eruptions on the hands, fingers, or feet. In the majority of cases these are due simply to eczema; others are signs of dermatitis due to external *irritants*, or are toxic eruptions due to ringworm infection of the toes, etc. Owing to the thickness of the horny layer on the hand, the vesicles cannot rupture as they would elsewhere, and remain in the skin for days like grains of boiled sago. The best treatment is calamine and lead lotion with liquor picis carbonis, and sometimes the addition of weekly doses of a quarter of a pastille of X-rays, not more than four in all.

It is claimed by Fitz-Patrick that a distinct form endemic in tropical Africa and India is caused by an anaërobic bacterium which attacks the palmar and interdigital aspects of the hands and the plantar aspects of the feet. The following ointment is said to be specific:

Coal tar	3 parts
Powdered charcoal	1 part
Zinc oxide	4 parts
Lanolin and vaseline . . .	12 parts

The ointment is rubbed well into the affected parts, and cotton gloves or socks are worn. In conjunction with this, resorcin soap must be used.

Dhobie's Itch (Tinea Cruris) and Pityriasis Versicolor

Ætiology and nomenclature.—By the lay public all epiphytic skin diseases in the tropics—more especially all forms of intertrigo—are spoken of as *dhobie's* (washerman's) *itch*, in the belief, probably not very well founded, that they are contracted from clothes which have been contaminated at the washerman's. There are many sources of ringworm infection in warm climates besides the much-maligned dhobie.

In the tropics, native children often exhibit dry, scurfy patches of ringworm on the scalp; and the skin of the trunk and limbs of adults is not infrequently affected with red, slightly raised, itching rings, or segments of rings, of trichophyton infection. In some cases these rings enclose areas that are many inches in diameter.

Pityriasis versicolor is also very common in the tropics. It is the usual cause of the pale, fawn-coloured, slightly scurfy patches so frequently a feature of the dark-skinned bodies of natives. On the dark-pigmented skins of negroes, Indians, and dark-complexioned Chinese, the patch of pityriasis—contrary to what obtains in Europeans and light-skinned Chinese—is usually paler than the healthy integument surrounding it. The pigment in the fungus and the profuse growth of the latter conceal, as a coat of paint might, the dark underlying natural pigment of the skin, which, moreover, in certain cases seems to be affected (either increased or decreased) by the action of the fungus. The disease is most commonly seen in young adults, is favoured by excessive perspiration, and especially by flannel underwear, and is rarely seen in the aged.

There are possibly several varieties of fungi involved in the production of pityriasis; besides *Microsporon furfur*, the best-known is *Microsporon mansoni*, of which a culture in maltose-agar produces black hemispherical colonies, and correspondingly black patches on the affected skin.

The expression dhobie's itch, although applied to any itching, ringworm-like affection of any part of the skin, most commonly refers to some form of epiphytic disease of the crutch or axilla. This infection has now become widespread in Great Britain and is endemic in most English public schools, where it is spread by infected clothes and water-closet seats. There are at least two species of parasites which in the tropics are prone to attack those situations, namely a trichophyton—*Epidermophyton inguinale*—and the *Microsporon minutissimum* of erythrasma.

E. inguinale is peculiar to man only; it is not easily cultivated, and grows slowly. On Sabouraud's agar medium it takes a week to develop, and appears first as powdery growth.

Symptoms.—The suffering to which certain forms of dhobie's itch give rise is often severe. In hot damp weather especially, the germs proliferate actively, producing, it may be, smart dermatitis. The affection begins usually as slightly raised, rounded and elevated papules which spread peripherally, producing a raised festooned border covered with thick scales. The excessive irritation thus set up leads to scratching and, very likely, from secondary bacterial invasion, to boils or small abscesses. The crutch, or axillæ, or both, are sometimes rendered so raw and tender that the patient may be unable to walk or even to dress. (Fig. 100.) It commonly extends backwards on the perineum and into the natal cleft about the anus. It often affects the skin under pendulous breasts and occasionally

forms patches resembling tinea circinata on the thighs. In some cases the clefts between the toes are attacked, giving rise to great itching. The irritations thus produced are usually worse at night, and may keep the patient awake for hours. Even in the absence of treatment, when the cold season comes round, the dermatitis and irritation subside spontaneously. The affected parts then become dry, pigmented, and scurfy, and the fungus remains quiescent until the return of the next hot weather.

Diagnosis.—The diagnosis of mycotic dermatitis is usually easily made. The festooned margin is almost conclusive. When doubt exists, recourse to the microscope may be necessary; but, owing to the inflamed condition of the parts, there may be much difficulty in

Fig. 100.—Dhobie's itch, symmetrical lesions in groins. (*Orig.*)

finding fungous elements even when the case is certainly epiphytic. A negative result is, however, not always conclusive against ringworm. The mycelial elements can usually be distinguished in epidermal scales soaked in liquor potassæ. It has to be distinguished from seborrhœic dermatitis, *intertrigo* and *flexural psoriasis*.

Treatment.—The patient should get two pairs of running shorts which should be worn on alternate days, the pair not in use being boiled. After a thorough use of soap and water, the application of *Vleminckx's solution* of sulphide of calcium (1 oz. quicklime, 2 oz. precipitated sulphur, 15 oz. water, boiled together in an earthenware vessel till reduced to 10 oz.; the clear sherry-coloured fluid being decanted after subsidence) every night for three or four times generally brings about a rapid cure. If the parts are inflamed and tender, the solution should be diluted to half- or quarter-strength for the first two applications. A preliminary soothing treatment by lead lotion, or an

ichthyol or hazeline cream, is desirable in such cases. A tincture of the leaves of *Cassia alata* painted on, or vigorous rubbing with the crushed leaves themselves, is equally successful. If these fail, chrysophanic-acid ointment, 20 gr. to the ounce of vaseline, rubbed in twice a day till a slight erythema shows at the edge of the diseased patch, is almost invariably successful. When prescribing chrysophanic acid the physician must be careful to inform the patient of its staining effect on clothes; to warn him to stop its use as soon as the erythematous ring shows, and to be careful not to apply the ointment to the face.

More conveniently, chrysophanic acid may be prescribed in the following form with gutta-percha, and should be painted on with a brush on alternate nights.

Acid. chrysophan. . .	gr.xx	(1·296 grm.)
Chlorof. . . .	ʒi	(3·5 c.c.)
Liq. gutta-perchæ . .	℥i	(28·42 c.c.)

Cignolin (Bayer) is a synthetic chrysarobin and is useful in all fungoid skin affections, in fungus of the nails, cheiropompholyx, and in psoriasis. Cignolin is apparently free from toxic action on the kidneys and in neat concentrations it can be applied to the scalp without any danger of conjunctivitis. The prescription is cadojel (a proprietary tar preparation), 1 grm.; cignolini, 0·1–0·2 grm.; benzol, 10 grm. If cadojel is not obtainable, a suitable formula is:

Ol. cadin. (deod.) . . .	♏xl	(2·368 c.c.)
Cignolin	gr.iv	(0·259 grm.)
Benzol. rect.	℥i	(28·42 c.c.)

The combination of cignolin and tar follows the indications closely, for the former has a parasiticidal action and the latter is unrivalled for its soothing properties.

The method of application is very simple, the affected areas being painted with the solution twice daily and then covered with strips of gauze. If there is too much irritation, then the painted areas are further protected with a thin layer of Lassar's paste or calamine lotion.

The following are the other prescriptions of Cignolin which may be used for this or any other fungus affection.

1.	Cignolin	gr.x	(0·648 grm.)
	Chlorof. meth. ad . . .	℥i	(28·42 c.c.)
	Ft. sol. = Cignolin paint.		
	Cignolin	gr.iv	(0·259 grm.)
	Zinc. oxid.	ʒss	(1·944 grm.)
	Ol. oliv. ad	℥ss	(14·21 c.c.)
	Ft. unguentum.		
3.	Cignolin	gr.ss	(0·032 grm.)
	Liq. carb. deterg. . . .	ʒss	(1·176 c.c.)
	Acid. salicyl..	gr.iii	(0·194 grm.)
	Paraff. moll. ad . . .	℥ss	(15·55 grm.)
	Ft. unguentum.		

4. Cignolin	. . . .	gr.v	(0·324 grm.)
Ichthyol .	. . . .	ʒss	(1·944 grm.)
Paraff. moll. ad	. . .	℥i	(31·1 grm.)

Ft. unguentum

Hallow (1936) endorses the value of cignolin treatment in his account of 310 cases treated in this manner. The patient should be isolated and kept in clean pyjamas during treatment. For three days cignolin 2 per cent. in soft paraffin is applied with bandages; even if one thigh only is affected, both should be treated. At the end of this period, only disinfected or non-infected clothing should be worn, and, as an additional precaution, unguentum acid. benz. should be applied nightly to the treated areas.

Tincture of merthiolate (Eli Lilly & Co.) is also effective (p. 692).

For the ringworms of the thick-skinned natives, linimentum iodi freely applied, and of double strength, is the best, speediest, and most efficient remedy, but it is too irritating and painful for the European skin.

During treatment the wearing of short cotton bathing-drawers is recommended.

Prophylaxis.—The various forms of crutch dhobie's itch may be avoided by wearing next the skin short cotton bathing-drawers and changing them daily, at the same time powdering, after the daily bath, the axillæ and crutch with equal parts of boric acid, oxide of zinc, and starch.

Ringworm of the Feet (Hongkong Foot, Brocq's Eczema Tinea Pedis)

A peculiarly intractable infection of the soles of the feet occurring especially amongst Europeans, is commonly observed in China and is known locally as "Hongkong foot." This mycotic infection, as identified by Dold, is believed to be a variety of *Epidermophyton inguinale*, or, according to Beintemar, *E. interdigitale*. It occurs especially during the summer months and appears as deep-seated vesicles about the inner margin of the hollow of the sole, or on, or between, the toes at their proximal extremities; or as a macerated condition of the skin of the interdigital clefts and of the contiguous surface: scaling of the skin with persistent and intolerable itching is a marked feature, and it often becomes secondarily infected (Fig. 101). Often a mycotic infection of the nails and the palms of the hands is associated with it. A similar condition has been described as occurring in Turkish baths in England by Whitfield, and in swimming baths in the Southern United States, as well as among bathers in Holland. As a preventive measure the application of the following lotion is recommended:

Liq. formaldehyde (40-per-cent.)		ʒi	(3·5 c.c.)
Acid. salicyl.	. . . . .	ʒi	(3·5 c.c.)
Alcohol and water equal parts	.	℥viii	(227·36 c.c.)

Treatment.—The application of Whitfield's ointment is recommended: Salicylic acid 1, benzoic acid 1, coco-nut oil 12, soft paraffin 16 parts, after the feet have been soaked in hot water. This ointment must be persisted with for three weeks or more.

The various preparations of *Cignolin* are also useful, as well as a sulphur preparation such as *Mitigal* (Bayer).

A powerful disinfectant which can be used for this purpose is *paranitrophenol* (I.C.I.). It is a brown powder and is used in concentrated form. The feet are first soaked for half an hour and dried. The stain can be removed by the application of a strong solution of

Fig. 101.—Ringworm of the foot. (*Editor's Case.*)

bicarbonate of soda. A very simple treatment, said to be efficacious, is painting the interdigital clefts with 2-per-cent. *mercurochrome* every night for two to three weeks. Another preparation which can be recommended is *Merthiolate cream* (Eli Lilly & Co.) and also tincture of merthiolate, a solution of merthiolate in spirit, which sinks deep into the affected skin and thereby kills off the spores of the fungus. Montel recommends *rubiazol*, injected intramuscularly, or *septazine* intravenously.

Macleod recommends bathing or paddling in sea-water.

Infected patients should take careful precautions against the spread of the fungus, and should wear special slippers in the bathroom. Loofah soles and bath towels are recommended as they can be sterilized by washing.

Ringworm of the Nails (*Tinea Unguium*)

This is a mycotic infection of the nails and is a comparatively common, and extremely intractable, condition in Europeans, especially in India and China; it is a singularly persistent infection and may last for twenty years or more. It may occur as an independent affection or secondary to ringworm of the skin, scalp, or beard, and is often found in association with tinea cruris. The nails of both hands and feet may be attacked or single ones of each member. The fungus is a trichophyton, usually *Epidermophyton inguinale;* it is never caused by a microsporon.

The fungus first attacks the epidermis of the nail-bed and gradually invades the nail matrix. In doing so it causes considerable discoloration, ridging and fissuring of the nail itself, which becomes opaque with a brittle, frayed edge. The fungus may pass from the skin over the nail-fold and in this manner reach the matrix.

Diagnosis.—The appearance of the affected nail is not sufficiently characteristic to be distinguished without microscopic examination. The disease is generally well advanced before it can be recognized. For microscopic diagnosis, scrapings of the nail are boiled in liquor potassæ or left to soak for twenty-four hours. The scrapings themselves should be made as thin as possible with a piece of glass. The fungus can then be recognized in the softened nail debris, especially in small dark hæmorrhagic spots. The diseases liable to be confused with ringworm of the nails are *eczema*, *syphilis* and, especially, *psoriasis*.

Treatment.—In the early stages when the lunule is attacked, the disease may be stamped out by softening the affected portion with solution of potash and painting with tincture of iodine or with a 2-per-cent. solution of corrosive sublimate in alcohol, twice daily. When the nail is completely involved, cure is almost impossible save by extirpation or by avulsion. The result is, however, disappointing as the new nail usually becomes infected in turn. After removal the thickened nail-bed should be scraped and the matrix dressed with a parasitical ointment:

Acid. salicyl.	gr.xxx (1·944 grm.)
Hydrarg. ammon.	gr.xv (0·097 grm.)
Vaseline	℥i (31·1 grm.)

The shedding of the nails by application of X-rays is unsatisfactory. Less severe cases are treated by softening the nail-plate by wearing finger-stalls of rubber containing soft soap for a few days; the softened nail is then scraped down as far as possible with glass, followed each time by the application of lint soaked in Sabouraud's iodine (iodine 5, potassium iodide 1, water 100), which should be kept in position by a loose rubber finger-stall.

Tinea Imbricata

Synonym.—Tokelau Ringworm.

Geographical distribution.—The affection is principally met with in the Eastern Archipelago and in the islands of the South Pacific, where it affects a large proportion of the population. It has been found to extend westwards as far as Burma, and northwards as far as Formosa and Foochow on the coast of China. Cases have been reported from Central Africa, and it occurs in the interior of Brazil. Once introduced, it spreads very rapidly in countries with a damp, equable climate and a temperature of 80–90° F. Very high or very low temperatures and a dry atmosphere are inimical to its extension.

Ætiology.—On detaching a scale and placing it under the microscope, after moistening with liquor potassæ, a trichophyton-like fungus can be seen in enormous profusion. The parasite evidently lies between epidermis and rete, and by its abundance causes the former to peel up. As the fungus does not die out in the skin travelled over, it burrows under the young epithelium almost as soon as the latter is reproduced. Hence the peculiar concentric scaling and the persistency of the disease throughout the area involved. When the scales are washed off by the vigorous use of soft soap and hot water, the surface of the skin is seen to be covered with parallel lines of a brownish colour—evidently the slightly pigmented fungus proliferating and advancing under the young epidermis.

The parasite, said by Castellani to be of two species, *Endodermophyton concentricum* and *E. indicum*, can be cultured by immersing the scales in alcohol for five to ten minutes and then placing them, one scale to each tube, in glucose broth. After five or ten days the scales, if uncontaminated, are transferred to solid media, and growth takes place in three or four weeks.

Symptoms.—Tinea imbricata may at first be confined to one or two spots on the surface of the body; usually, in a short time it comes to occupy a very large area. It does not generally affect the soles and palms, although it may do so; nor is the scalp a favourite site. Baker remarks that it avoids the crutch and the axillæ. With these exceptions it may, and commonly does, sweep over and keep its hold on almost the entire surface of the body, so that after a year or two a large part of the body is covered with the dry, tissue-paper-like scales, arranged in more or less confused systems of concentric parallel lines. This arrangement of the scales is absolutely characteristic of the disease, as may be seen from Plate XXIII.

An inoculation experiment readily explains the production of the scales, their concentric parallel arrangement, and the mode of extension of the patches. About ten days after the successful inoculation of a healthy skin with tinea imbricata, the epidermis at the seat of inoculation is seen to be very slightly raised and to have a brownish tinge. Presently the centre of this brownish patch—perhaps a quarter of an inch in diameter—gives way, and a ring of scaling epidermis, attached at the periphery, but free, ragged, and slightly elevated towards the

TINEA IMBRICATA.

(By permission of Medical Department of Sarawak Government.)

PLATE XXIII

PINTA.

(Photo: Dineen, San Francisco.)

PLATE XXIV

centre of the spot, is formed. In a few days this ring of epidermis has extended so as to include a larger area.

The scales, if not broken by rubbing, may attain considerable length and breadth; but, of course, their dimensions are in some degree determined by the amount of friction to which they are subjected. Usually they are largest between the shoulders—that is, where the patient has a difficulty in scratching himself. The lines of scales are from $\frac{1}{8}$ to $\frac{1}{2}$ in. apart. The hair of the scalp is not injured.

Diagnosis.—From *ordinary ringworm*, tinea imbricata is easily distinguished by the absence of marked inflammation or congestion of the rings, by the abundance of the fungus, by the large size of the scales, by the concentric arrangement of the many rings or systems of rings, by the non-implication of the hair, and by the avoidance of crutch and axillæ. From *ichthyosis* it is distinguished by the concentric arrangement of the scaling, by the peripheral attachment of the scales, and by the presence of an abundance of fungus elements.

Treatment.—The best treatment for tinea imbricata in natives is the free application of linimentum iodi; its action is said to be increased by the addition of salicylic acid, 15 gr. to the ounce. Limited patches may be treated with chrysophanic-acid ointment (20 gr. to the ounce), or by the more modern preparation, Cignolin. Clothes should be boiled or burned.

Prophylaxis.—Daniels related that tinea imbricata is a comparatively rare disease in Tonga. This circumstance the natives attribute to their custom of oiling the body with coco-nut oil. Since the Fijians adopted this practice the disease has become somewhat less prevalent among them. Personal cleanliness, and the immediate and active treatment of any scaling spot, should be carefully practised in the endemic countries. Amongst certain Central African tribes in women, who oil their bodies, it has never been observed, whereas the men, who do not adopt this custom, are subject to the disease.

In Tahiti the use of chrysophanic acid is now general among the natives; as a consequence, the disease is less prevalent there than it was only a few years ago.

Pinta

Synonyms.—Caraate; Mal del Pinto.

Definition.—An epiphytic disease characterized by peculiar pigmented patches on the skin.

Geographical distribution.—Pinta occurs in certain districts in tropica America, especially along the river banks—in Mexico, Central America, Venezuela, Colombia, Bolivia, and in one or two places in Peru, Chile, Guatemala, Honduras, and Brazil.

Ætiology.—If one of the scales is moistened with liquor potassæ and placed under the microscope, black spores and a white, highly

refracting mycelium are found. (Fig. 102.) The spores are round or oval, measuring 8 μ to 12 μ in diameter. Abundant pigment is seen floating in a yellowish fluid in the interior of the spore. The mycelial

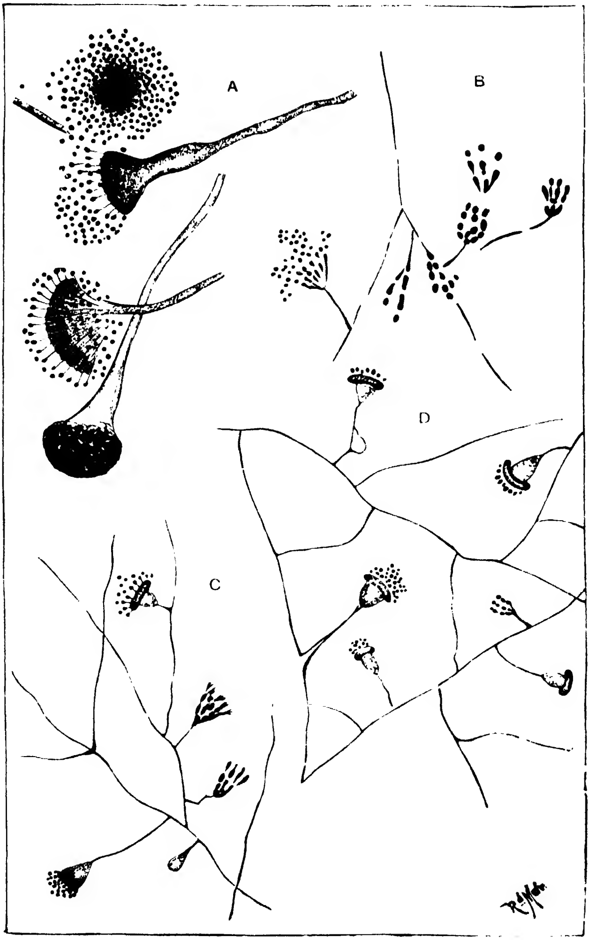


Fig. 102.—Fructification of cryptogamic epiphytes in pinta.
(*After Montoya y Florez.*)

A, Red pinta; B, dark-violet pinta; C, grey-violet pinta; D, blue pinta.

filaments are short, non-branching, tapering from a broad base to a blunt point by which each filament is attached to a single spore, like the stalk to a cherry. The mycelium measures from 18 μ to 20 μ in length by 2 μ in breadth. The differences in the colour of the patches

probably depend on differences in the pigmentation, or kind, of the fungus. Pardo-Castelli in Cuba has suggested that many of the lesions ascribed to pinta are in reality depigmented areas due to syphilitic infection.

Symptoms.—Pinta commences at one or two points, the rest of the surface of the skin becoming infected in turn by extension or by autocontagion. At first the hands or face, or some other exposed parts, are attacked. The original patch becomes hyperpigmented owing to active pigment-formation, but later it becomes white, red, blue, or black. It gradually increases in size, becoming scurfy and itchy, particularly when the surface is warm. As the patches spread they assume a variety of shapes. Fresh spots appear in the region of the parent spots, into which, in course of time, they tend to merge, so that ultimately large patches of discoloured skin are formed. (Plate XXIV.) The palms of the hands and the soles of the feet are not attacked. On the scalp becoming affected the hair turns white and thin, and ultimately falls out. When fully developed the disease produces a very grotesque appearance. It is probable that the white patches in a proportion of cases are not epiphytic, as they neither itch nor desquamate; very likely they are ordinary leucoderma, possibly brought about through disturbance of the natural pigmentation by a parasite which subsequently died out. Neither sensation nor the glandular functions of the skin are affected. In consequence of the scratching, the implicated parts may become cracked or ulcerated.

Two types of the disease have been named—the superficial epidermic and the deep epidermic, the former being represented by black and blue patches which spread rapidly, the latter including the red and white patches, apparently involving the rete and deeper layers of the epidermis, spreading more slowly, and, at the same time, being more difficult to cure. The various forms and colours may concur in the same individual; but a given patch, once established, does not change colour.

Pinta is contagious. It attacks both sexes and any age. Unless properly treated it may last for years. Want of personal cleanliness has a great deal to do with the prevalence of pinta in the countries mentioned, for it is seldom met with in Europeans or in prosperous negroes. In some districts it is comparatively rare, while in others nearly the entire population is affected. The patient emits an offensive odour not unlike that of dirty linen. No constitutional disturbance is provoked.

Diagnosis.—This disease is readily diagnosed from leprosy by the absence of anæsthesia in the patches, and by the colour of the spots; from erythrasma, from ringworm, and from pityriasis versicolor by the colour and the microscopic characters of the fungus.

Treatment.—Chrysophanic acid, preparations of sulphur, liniment of iodine, and other epiphyticides are indicated. Cleanliness and the destruction of old clothes are indispensable.

Trichosporosis

Synonym.—Piedra.

This peculiar disease of the hair is very common in certain districts of Brazil, Colombia and British Guiana. So far as is known, it is virtually confined to the inhabitants of those countries, of whom a considerable proportion, both male and female, and apparently belonging to all the races represented there, are affected. It is commoner in native women, but has been observed on the eyelashes, beard, and scalp.

The hairs are dotted over at irregular intervals with numerous (1 to 10 or more in a hair 60 cm. in length) minute, gritty nodosities, which feel like sand grains—hence "piedra"—sandy. These, barely visible to the naked eye, are distinctly perceptible to the touch when the hair is drawn between finger and thumb. The affected hairs are

Fig. 103. Human hair (magnified) affected with *Trichosporon beigeli*. (*Orig. preparation. Photo by Dr. H. B. Newham.*)

bent and twisted, and tend to produce matting and knotting. The little nodosities—which, though very firm, are not so hard as the name piedra (a stone) would indicate, being easily cut through with a sharp knife or scissors—are paler than the hair which they surround, or partly surround, like a sheath. They are situated in the extrafollicular portion of the hair, and vary in number from one to ten or more. When a comb is drawn through the hair, a sort of crepitation is produced, doubtless by the friction against the hard particles.

In Brazil piedra is known as far as Bahia, where Horta published a monograph which remains a model of precise observation

Ætiology.—Under the microscope the excrescences are found to consist of a number of spore-like bodies, *Trichosporon giganteum*, easily made apparent by soaking the hair in liquor potassæ after washing in ether. From mutual pressure the spores, which are twins the size of trichophyton spores and remarkably refringent, are polehedral, and together form a sort of tessellated mosaic, the elements of which seem to be held together by a greenish soluble cementicy which a number of minute bacteria-like rods are incorporated. The shaft of the hair—not eroded or affected in any way—can be seen intact through the encrusting fungus. *T. giganteum* is easily cultivated

on ordinary media. It liquefies gelatin in ten or twelve days. The smallest spores measure 2-5 μ, the largest up to 12 μ. Piedra is supposed by some to be induced by the mucilaginous hair applications in vogue among the Colombians. Langeron has suggested that the correct name for the parasite should be *Piedra hortai* and he considers that it is probably an epiphyte analogous to certain epiphytic fungi which grow on the leaves in the forests of Central America.

Diagnosis.—Although Juhel-Rénoy has given to piedra the name "trichomycose nodulaire," the condition must not be confounded with trichomycosis nodosa, which is a different affection and common enough on the axillary, scrotal, and face hair in Europe and elsewhere. Neither must it be confounded with trichorexis nodosa, non-parasitic disease of the hair-shaft, which is split up at different points into brush-like bundles of fibres, and is thus easily fractured; nor with moniliform hair, a congenital, hereditary, and non-parasitic condition.

Treatment.—Cleanliness, the free use of soap, and the application of some epiphyticide should suffice for cure; but should such means fail, doubtless shaving the scalp would be effectual.

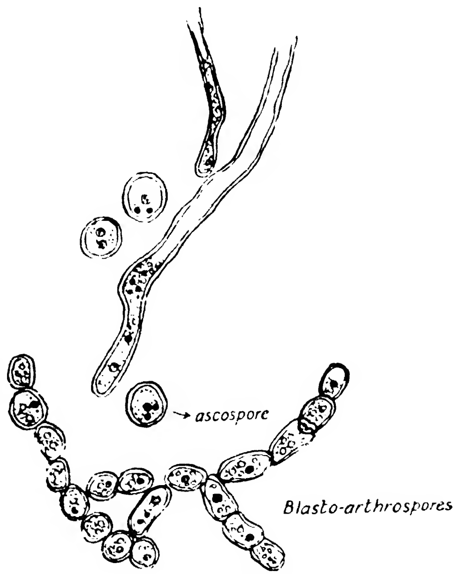


Fig. 104.—Fungus elements of *T. beigeli*. (*Orig.*)

TRICHOMYCOSIS

Synonyms.—Trichonocardiasis; Trichomycosis nodosa.

Trichomycosis is a fungous disease of the hair, found in Central Africa and Asia, which in many ways resembles piedra. It may produce skin irritation and staining of the clothes. The shafts of the hairs, more especially those in the axilla, are attacked. The parasite is *Trichosporon beigeli* (Rabenhorst, 1867). This has been thoroughly studied by P. Vuillemin (1902). On the hairs it produces irregular nodosities containing the fungus elements, each 3 μ to 5 μ in length. In cultures mycelial formation takes place, composed of arthrospores, giving rise to blastospores, and in older cultures to ascospores. The fungus is easily cultivated on Sabouraud's medium, or beer-wort.

This fungus, which was first discovered in London by Beigel in 1862, has been found occasionally in Europe, and is quite common in Japan. It may attack the beard and moustache, which may become matted together so that they cannot be combed out. The affected part emits a peculiar odour, as in the Editor's case from which these illustrations are taken. (Figs. 103, 104.) The hairs have a beaded or nodular appearance and the deposit may vary considerably in colour. The disease may spread to the skin and cause a severe intertrigo.

Microscopically the lesions are shown to consist of a mass of polygonal cells, yellowish-green to brown in colour, with a definite cell-wall. The cells of a mycelial thread are separated from one another by thick black cell-walls between which there is little intercellular substance.

Treatment.—The affected hair should be bathed twice daily with a lotion consisting of 1 dr. of formalin to 6 oz. of rectified spirit, reinforced by 2 per cent. sulphur ointment. The affected surrounding skin should be rubbed with mercurial ointment.

IV. SKIN DISEASES CAUSED BY ANIMALS

The Chigger, or Sandflea

This insect, formerly confined to the tropical parts of America (30° N. to 30° S.) and to the West Indies, appeared on the West Coast of Africa for the first time about the year 1872. Since that date it has spread all over the tropical parts of that continent, and even to some of the adjacent islands—Madagascar, for example. As a cause of suffering, invaliding, and indirectly of death, it is an insect of some importance. It is now extremely prevalent on the East Coast of Africa, and is causing a large amount of invaliding among the Indian coolies there, by whom it has been introduced into India. Further east it is found in Karachi, but in no other part of India.

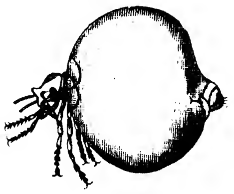


Fig. 105.—Chigger, impregnated female. × 10. (*Blanchard.*)

The chigger (*Tunga penetrans*) is not unlike the common flea (*Pulex irritans*) either in appearance or, with one exception, in habit. It is somewhat smaller in size (1 mm.), the head being proportionately larger and the abdomen deeper than in the latter insect. In colour it is red or reddish brown. Like the flea, its favourite haunt is dry, sandy soil, the dust and ashes in badly kept native huts, the stables of cattle, poultry pens, and the like. It greedily attacks all warm-blooded animals, including birds and man. Until impregnated, the female, like the male, is free, feeding intermittently as opportunity offers. So soon as she becomes impregnated she avails herself of the first warm-blooded animal she encounters to burrow diagonally into its skin, where, being well

nourished by the blood, she proceeds to ovulation. By the end of this process her abdomen, in consequence of the growth of the eggs it contains, has attained the size of a small pea. (Figs. 105, 106.) As seen in Fig. 106, the chigger within the epidermis enters the stratum lucidum, which it invades and pushes before it. The epithelial layer becomes attenuated. The parasite becomes anchored in the corium by means of chitinous excrescences which stick out into the surrounding tissues. The first anterior and the two posterior segments do not participate in the enlargement, the latter acting as a plug to the little hole made by the flea on entering the skin. When the eggs are mature they are expelled by strands of muscular fibres which intersect the abdomen, and fall on the ground. According to Hicks, the larva hatches on the third or fourth day; the first moult occurs on the fifth to eighth day and preparation for pupation on the sixth to seventeenth days. The larva pupates at the same time, and the imago usually emerges about the seventeenth day.

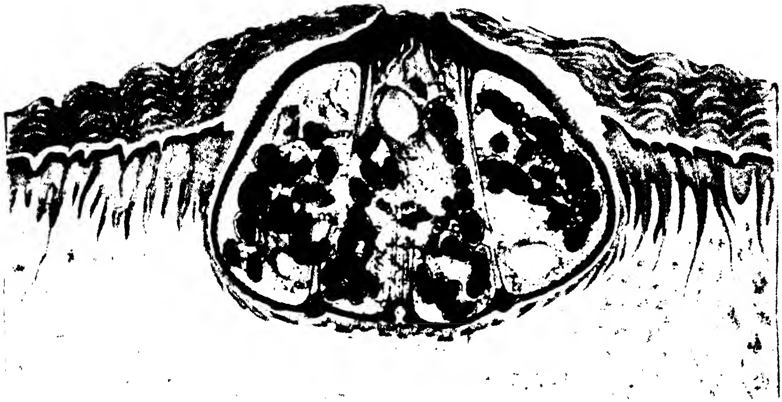


Fig. 106. Section of female chigger in the stratum lucidum of the skin.
(*Fülleborn, Arch. für Schiffs-und Tropenhyg.*)

Generic name of the chigger.—Until recently known as *Sarcopsylla* Westwood, 1840, or *Dermatophylus* Lucas, 1839, the sandflea, as Rothschild pointed out, should bear the generic name of *Tunga*, as it was figured as *T. penetrans* by Jarocki in 1838. It becomes, therefore, by the law of priority, *Tunga penetrans.*

During her gestation the chigger causes a considerable amount of irritation. In consequence of this, pus forms around her distended abdomen, which now raises the inflamed integument into a pea-like elevation. After the eggs are laid (according to some, before this process) the superjacent skin ulcerates and the chigger is expelled, leaving a small sore which may be infected by some pathogenic micro-organism, such as the bacterium of phagedæna or of tetanus, with grave consequences. (Fig. 107.)

Being nearest the ground, the feet are the part most commonly

infested by chiggers. The soles (Fig. 108), the skin between the toes, and that at the roots of the nails are favourite situations. Other parts of the body are by no means exempt ; the scrotum, the penis, the skin around the anus, the thighs, and even the hands and face, are often attacked. Usually only one or two chiggers are found at a time ; occasionally they are present in hundreds, the little pits left after their extraction, or expulsion, being sometimes so closely set that parts of the surface may look like a honeycomb.

Treatment.—In chigger regions the houses, particularly the ground floors, must be frequently swept and the accumulation of dust and debris prevented. The housing of cattle, pigs, and poultry demands

Fig. 107.—Septic lesions of foot caused by chiggers. (*Orig.*)

the same precautions. The floors should often be sprinkled with carbolic water, pyrethrum powder, or similar insecticide, and walking bare-footed must be avoided. Bathing must be practised daily, and any chiggers that may have fastened themselves on the skin at once removed. They may be killed by pricking them with a needle, or by the application of chloroform, turpentine, mercurial ointment, or similar means, after which they are expelled by ulceration. The best treatment, however, is not to wait for ulceration, but to enlarge the orifice of entrance with a sharp, clean needle and neatly to enucleate the insect entire. Some native women, from long practice, are experts at this little operation. The part must be dressed antiseptically and protected until healed. Europeans living in an endemic district should wear high boots. A daily inspection of the feet, especially

under the nails, is advisable. Should any black dot be discovered, the chigger should at once be removed.

Prophylaxis.—If avoidable, camps should not be formed in chigger-infested spots or in the neighbourhood of native villages. The camping-ground should be swept or, if necessary, fired; the floors of huts and tents may be sprayed with insecticides and naphthaline, and native tobacco dusted inside boots or shoes. Balfour

Fig. 108.—Chiggers in sole of foot. (*Photo: Dr. C. W. Daniels.*)

recommends that the feet be rubbed thoroughly with a mixture consisting of 5 drops of lysol, or liq. cresoli sap., in 1 oz. of vaseline. Special attention should be paid to the interdigital clefts. Pigs should not be kept in the vicinity of dwelling-houses, as these animals are severely attacked by chiggers.

Acarine Dermatosis

Several forms of mites inhabiting sugar, grain, or copra may live as temporary parasites on the skin of man, and set up an intense irritation not unlike that produced by scabies. One of the most

familiar of these is "grocer's itch," set up by mites of the genus *Glycophagus*, which are common in raw sugar and cause an erythematous rash. Among the copra workers in Ceylon and the Pacific islands a similar skin affection is due to a *Tyroglyphus*. "Grain itch," an urticarial and papular eruption of the exposed parts of the

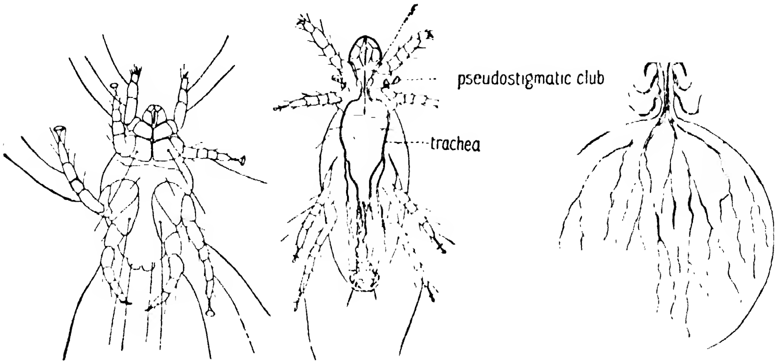


Fig. 109.—*Pediculoides ventricosus*. × 80. (*After Alcock.*)
A, Male; B, adult female; C, pregnant female with brood-sac.

body, is caused by *Pediculoides ventricosus* (Fig. 109, A, B, C) in those who handle grain, cotton-seeds, or beans. The presence of these mites gives rise to a severe pruritis. Preventive treatment consists in the application of beta-naphthol ointment (5-per-cent.), and the employment of dilute carbolic acid to kill off the mites.

Section VIII.—LOCAL DISEASES

CHAPTER XL

TROPICAL PYOMYOSITIS—RHINOSPORIDIOSIS—AINHUM—BIG HEEL—ONYALAI—CHIUFA

I. Tropical Pyomyositis

Synonyms.—Myositis Purulenta Tropica; Tropical Myositis; "Bung-pagga" (Patton).

Geographical distribution.—In 1912 H. H. Scott described this disease in Jamaica. Deep intramuscular abscesses were associated with pyrexia, and a striking feature was the hard swellings set up by enormous collections of serous fluid. A small bacillus was isolated which he named *B. serofaciens*.

In the same year Külz found intramuscular abscesses very common in the Cameroons: and in Duala, in 1907–1908, out of 386 natives, 18 were operated for intramuscular abscesses, and out of 86 Europeans, 5 were thus treated. In natives abscesses were multiple, in Europeans usually single, and they varied in size up to that of a hen's egg. He believed that these cases of purulent myositis were really due to *Loa loa* infections.

In 1913, Wise and Minnett in British Guiana described what was obviously the same condition, and they failed to find remains of adult filariæ in the pus, though in seven filaria embryos were discovered. Recurrence of abscesses in the same patient was a feature of the disease. In most instances streptococci were isolated from the pus.

Ziemann (1913) described an exactly similar form of intramuscular suppuration in New Guinea, and claims that already, in 1904, he recognized the disease as one *sui generis* and distinct from filariasis. In 1917, E. L. Walker reported upon cases from Brazil. Commes in 1918 met with this disease in French West Africa, where it had previously been noted by Bouffard. In 1922, Laigret and Lefrou remarked upon the deep chocolate colour of the pus, resembling almost liver-pus in this respect, in French Equatorial Africa. Tanon and Jamot (1926) found it common in the Cameroons during the War, when it was known as "*lambo lambo*." Summaries of our knowledge on this subject have been made by Appel (1921) from the German, and Connal (1930) from the British view-point, and Gibler (1922) gives further details of pyomyositis in Northern Australia and Papua, and James in the Solomon Islands. Van Steenis (1931) has recognized the same disease in Java. P. A. Buxton (1928) has written a very complete account of myositis as he observed it in Samoa, and is convinced on ætiological grounds that myositis is distinct from deep suppuration sometimes observed in filariasis. This acute myositis

is of considerable importance in Samoa, and was observed in Europeans, Samoans, half-castes, Chinese, and Melanesians. He found that pulmonary complications were not infrequent, the abscesses were invariably intramuscular, and suppurative and non-suppurative lesions were common, while *Staphylococcus aureus* was the organism responsible. Grace and Grace (1931) investigated an outbreak of this condition which amounted to an epidemic, in the island of St. Kitts. The outbreak affected more than 300 individuals, with a death-rate of 10 per cent. Some cases resembled those of septicæmia. The infection was regarded by Pawan to be secondary streptococcal and staphylococcal infection in filaria-infected subjects. Grace considered the causal organism to be a hæmolytic streptococcus that was present also in the throats of those attacked.

The following types of the disease can now be distinguished :

(*a*) Acute non-suppurative.
(*b*) Acute suppurative.
(*c*) Acute suppurative with relapses.
(*d*) Acute suppurative with pyæmia.
(*e*) Hyperacute ending in septicæmia.

Associated infections.—Pyomyositis is more apt to occur in persons who are debilitated as the result of some other longstanding infection. In the Editor's experience this has been either ancylostomiasis, malaria, and, in a proportion of cases, syphilis. In his series of cases the Wassermann reaction has been positive in 50 per cent. One of the chief aims of treatment should be the eradication of these concomitant infections, and vigorous antisyphilitic treatment with salvarsan and bismuth should be applied.

Ætiology.—The attention of practitioners in the tropics has been drawn for some time past to the frequency and peculiarities of deeply-seated intramuscular abscesses in natives. It had been assumed, apparently on insecure grounds, that this serious disease, which often leads to death by metastatic pyæmic manifestations, was in fact a complication of *Wuchereria bancrofti* infection, and this until recently was the Editor's opinion, but now he is willing to admit that pyomyositis has no intimate relationship to filariasis and occurs as an independent condition, even in those countries where filarial disease does not exist. He has seen cases of the disease in Europeans, Chinese, Japanese, Indians, Negroes, and Pacific Islanders.

Two forms of this disease appear to exist. The one consisting of hard, indurated, painful, inflammatory swellings, situated deep in the muscular tissue, which are caused by the collection of serous fluid ; the other associated with wide and extensive suppuration. The organism concerned, in the Editor's experience, has been *Staphylococcus pyogenes aureus* and *albus*, and occasionally *Streptococcus pyogenes*. The Editor, in 1910 in Fiji, described eight cases of spontaneous, deep intramuscular abscesses in Fijians who were known to be infected with *W. bancrofti*. Intramuscular abscesses of this description are apparently common in Fijians in the gastrocnemius muscle, in the popliteal space, in the adductor muscles in the groin, and in the substance of the serratus magnus and latissimus dorsi muscles.

But Sayers has successfully shown in the Solomon Islands that the majority of these deep-seated abscesses, even in such a country where filariasis is common, do not give a positive intradermal filaria test (Fairley).

Diagnosis.—The diagnosis of pyomyositis should not present any great difficulty, but it has to be differentiated from gummatous suppuration, filarial abscesses, glanders, melioidiosis, rheumatic nodules, and swellings. The possibility of confusion with plague, or even with trichinosis, may arise.

Treatment.—The course of events is well illustrated in the case of a European from British Guiana who was treated in 1931. The illness lasted over one year and commenced in the form of external boils, mostly in the feet and arms. Soon febrile attacks, associated with stiffness of the muscles, which were thought to be rheumatic in nature, appeared. Small hard nodules were noted on the leg, thigh, pectoral and submaxillary regions. The stiffness of the legs was due to diffuse indurated swellings in the extensor muscles, which were due to infiltration with serous fluid. During the seven months he was under the Editor's care no less than fifteen inflammatory swellings appeared in various parts of the body, associated with stiffness, pain, and pyrexia. The extensor muscles of the thigh moving the knee-joint were the seat of several large abscesses. The Wassermann reaction was strongly positive. There was a moderate leucocytosis of 15,000–19,000. From time to time inflammatory periosteal nodules appeared which could be demonstrated by means of X-rays, and there was synovitis of both knee-joints. Eventually a large abscess appeared in the right pectoralis major muscle which eventually led to partial necrosis of the eighth rib, which had to be resected. The organism responsible was found to be *Staphylococcus aureus*. The patient eventually recovered after eight surgical operations and prolonged antisyphilitic treatment with bismuth and neosalvarsan. Combined vaccine treatment with a vaccine of *Staphylococcus pyogenes aureus* was found to be fairly successful. Under modern conditions treatment with sulphanilamide drugs, notably Uleron (Bayer) 0·5 grm. tablets or 1·5–3 grm. daily for ten days, is indicated, and Earle has (1939) reported some cures with M. & B. 693 in Trinidad.

II. Rhinosporidiosis

Definition.—A disease due to a yeast-like organism, *Rhinosporidium seeberi*, which infects the mucous membrane of the nose, producing nasal polypi and tumours on the cheek, the conjunctiva, lachrymal sac, and uvula.

History.—*R. seeberi* was first described in Argentina (1896), and considered to be a protozoon allied to *Coccidium*. Subsequently it was found in nasal polypi by O'Kinealy in 1903, when the organism was described by Minchin and Fantham. Ashworth (1923) demonstrated that the organism is probably a yeast, or phycomycete.

This parasite has now been recorded from India, Ceylon, Argentina, and the United States.

Ætiology.—*Rhinosporidium seeberi* (Wernicke, 1903) is a spherical or oval non-motile organism which occurs in polypoid growths, usually lying between the connective-tissue cells. The earliest stages are about 6 μ in diameter, with a chitinous envelope, vacuolated cytoplasm, and a vesicular

nucleus containing a karyosome (Fig. 110, A, B). When fully-grown, the cyst, or sporangium, may measure 0·25–3 mm. in diameter, but when half-grown the nucleus commences to divide by binary fission till thousands are produced, of which the majority become daughter-spores, though a considerable proportion remain unchanged. The fully-formed sporangium (Fig. 110, C) finally bursts and discharges the spores, which are enclosed in chitinous envelopes; they then spread into the connective tissues *via* the lymph channels, and on their reaching suitable spots the trophic stage at once begins and the cycle is repeated.

Attempts at cultivation of the parasite have proved to be partially successful in Ashworth's hands, and multiplication of the spores took place, but very slowly, on Sabouraud's medium.

g. **110.**—*Rhinosporidium seeberi.* (*After Ashworth; by permission of Roy. Soc. of Edin.*)

A, Trophic stages. B, Section of a stage with 64 nuclei, 24 of which lie in this section. C, Sporangium from which spores are being discharged, accompanied by mucoid substance, through a wide orifice. The first spores to issue (those near the opening) are followed by the central spores. The peripheral spores lie in a fairly firm mucoid matrix. Stretching of the envelope, due to growth of the sporangium, has not only reduced its thickness, but has almost caused the disappearance of the thickened annulus round the pore.

The mode of transmission of this parasite is undetermined, but the occurrence of a closely related organism, *R. equi*, in the nasal cavities of the horse is suggestive.

Treatment consists in removing the polypi from the nares by means of a wire snare. Medical treatment would not appear to be indicated, although Wright has reported that the tumours disappear after intravenous injections of tartar emetic.

III. Rhinoscleroma

Rhinoscleroma (*Scleroma respiratorium*) (Fig. 111) is a well-marked disease in all its aspects, pathological or bacteriological. It has a world-wide distribution, but at the present day is much commoner in

the Tropics than elsewhere. Rhinoscleroma takes the form of spontaneous, painless, and exceedingly chronic, inflammatory growths occurring at any place in the respiratory passages from the nostrils to the hilum of the lung. Gross deformity of the nose or a narrowing or distortion of the respiratory passages results. Sometimes, too, perforation of the nasal septum is noted, and total destruction of the uvula. The process extends along the respiratory passages with little change in the surrounding tissues; on the whole it tends to form metastases with enlargement of the neighbouring lymphatic glands,

Fig. 111. Rhinoscleroma of two years' duration in an Egyptian woman.
(Dr. H. K. Griffin, Assiut, Egypt.)

but, in spite of this, the general health and condition of the patient remains unaffected.

Geographical distribution.—Rhinoscleroma is spread over widely distributed regions in special nests, or foci, but occurs all over the world. The most extensive region is in Eastern Europe, in Hungary, Poland, the Ukraine and the northern shores of the Black Sea and Caspian. Other foci have been noted at Tomsk in Siberia, and in Turkestan, Bengal, Java and Sumatra, central and southern France, Morocco, Egypt, North America (in New England states), Cuba, Mexico, Panama, Colombia, Brazil, Peru, and Chile.

Ætiology.—The cause of rhinoscleroma is undoubtedly the *Bacterium rhinoscleromatis* described by V. Frisch in 1882. It is closely related to *Bact. pneumoniæ*, and is usually Gram-negative. It is easily cultivated, and forms knob-like colonies on gelatin or agar, greyish in colour on the whole, and less conspicuous than *B. pneumoniæ*.

It usually coagulates milk, and it forms acid freely with lactose. In sections, it is found in hard fibrotic swellings in the nose, scattered throughout the mucosa and submucosa. It has so far been found impossible to reproduce the lesions by inoculation, either in man or in animals. In fact, it exhibits a very low order of pathogenicity for laboratory animals, with the exception of mice.

It has to be differentiated from other encapsulated pneumococcus-like organisms in the nose.

Pathology.—Pathologically rhinoscleroma is characterized by a

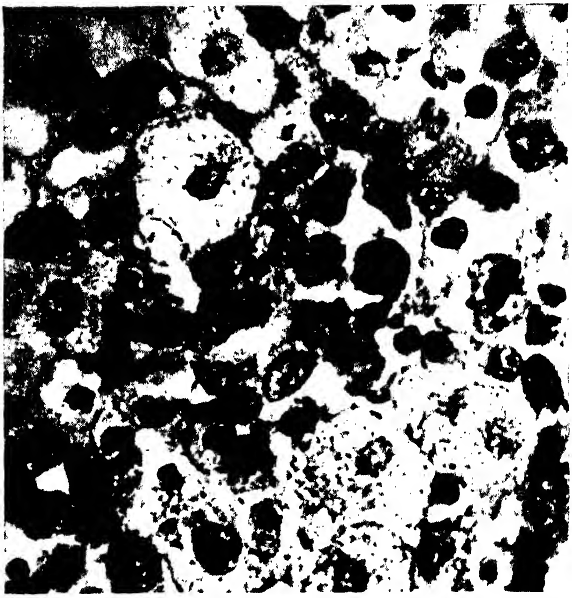


Fig. 112.—Rhinoscleroma : Photomicrograph of tissue, showing Mikulicz cells and general histological picture. (*Dr. H. K. Griffin.*)

peculiar form of plasma-cell infiltration typified by great density and the presence in the tumour of gaps or " fat-cells," which are found to consist of swollen cells with foamy cytoplasm (" foam-cells " or " Mikulicz cells ") (Fig. 112). Very frequently, also, hyaline-drop or Gram-positive " Russell's bodies," which occur in all kinds of degenerative tissues, and are probably derived from the plasma cells, are also present. The rhinoscleroma nodule is known as plasmoma (Unna) ; it never breaks down, but becomes progressively sclerosed.

Treatment.—The treatment of rhinoscleroma is mainly surgical and is directed to plastic operations to remove the unsightly outgrowths from the nose and lips.

Various other methods, the most important of which is X-ray

therapy, have been tried. The intravenous injection of tartar emetic, as in bilharziasis or ulcerating granuloma, has been advocated by some.

Fig. 113.—Ainhum.

It is a curious fact that complicating febrile diseases, such as erysipelas, typhoid or typhus fever, may cause the healing of rhinoscleromatous growths. This has led to a trial of inoculated malaria or protein-shock therapy, with encouraging results.

IV. Ainhum

This is a disease of a very peculiar character, affecting the toes, particularly the little toes, of negroes, East Indians, and other dark-skinned races, both in the Old and the New World. The name, derived from the Nago dialect, means "to saw or cut."

Symptoms.—The disease commences as a narrow groove in the skin, almost invariably on the inner and plantar side of the root of the little toe. It may occur in one foot only, or in both feet simultaneously, or it may affect one foot after the other. The groove, once started, deepens and extends gradually round the whole circumference of the toe. As it deepens—it may be, though not necessarily, with an amount of ulceration—the distal portion of the member is apt to swell to a considerable size, as if constricted by a ligature (Figs. 113, 114). There is little or no pain, although there may be inconvenience from the liability to injury to which the dangling and now everted toe is exposed. In the course of years the groove slowly deepens, and finally the toe drops off or is amputated. The groove may either correspond with a joint or may be formed over the continuity of a phalanx. In rare instances, after the two distal phalanges have dropped off or been amputated, the disease recurs in the stump, and the proximal phalanx in its turn is thrown off. Of the other toes, the fourth is the one which is most frequently affected; very rarely is the third, or second, or great toe attacked. In the Army Medical Museum at Washington, U.S.A., there is a wax model representing a case of this or a similar affection, in which all the toes had been thrown off and the disease was making progress in the leg.

Fig. 114.—Ainhum at its height.
(*Dr. A. B. Filho.*)

Occasionally, the terminal phalanx of the fifth digit of the hand has been found to be affected.

Ainhum is very rare in women or children, being most common in adult males. It runs its course in from one to ten or even more years.

On section, it is found as a rule, though not invariably, that the panniculus adiposus of the affected toe is much hypertrophied, that the bone is infiltrated with fatty matter, and that the other tissues are correspondingly degenerated. Sometimes the bone is thinned, or even altogether absorbed. At the seat of constriction a line of hypertrophy of the epithelial layers, and of atrophy of the papillary layer of the skin, together with a band of fibrous tissue, more or less intimately connected with the derma, surrounds, in whole or in part, the narrow pedicle.

Treatment.—It has been suggested that division of the constricting fibrous band would delay the evolution of the disease. In the early stage this might be tried. When troublesome, the affected toe should be amputated. It is said that the application of salicylic ointment delays the process in the earlier stages of the disease (Moreira).

V. Big Heel, or Endemic Hypertrophy of the Os Calcis

Maclean described a peculiar form of enlargement of the os calcis which he observed at Kaziankor, Gold Coast, among Fantis and Kroos. The disease begins somewhat suddenly, being preceded by fever, and attended by pain and tenderness which reach their maximum in about a month, gradually diminishing during the succeeding one or two months. Concurrently with the pain a swelling of the external surface of the os calcis, rarely of the other tarsal bones, makes its appearance.

Maxwell has reported a similar condition in natives of Formosa. As in Maclean's cases, the patients were young adults from twenty to twenty-five years of age.

VI. Onyalai

Under this title Massey and, later, Wellman (1904), originally described a peculiar disease occurring among the natives of Portuguese West Africa. Since then it has been recognized in East Africa, on the Congo, and in Northern Rhodesia, where it is known as "Chilopa," or "Akembe," (bleeding disease—Wallace). On the Congo it is known as "Kafindo." It is not usually seen outside Africa, though Preston Maxwell in 1901 described a somewhat similar disease in the Fokien region of South China. It is characterized by the formation of a number of vesicles, distended with blood from $\frac{1}{4}$ to $\frac{3}{4}$ in. in diameter, on the hard palate and on the inside of the cheeks. Some of the vesicles are umbilicated. They differ from ordinary blood blisters by the presence of numerous trabeculæ and by the semi-coagulation of the contents which makes the vesicle difficult to empty. The urine, apparently invariably, contains free blood. Numbness and pains in various parts of the body may be noted. There may be mental confusion and the parotids may be swollen and tender. Occasionally the disease is accompanied by fever and, although Massey's original case, with one exception, recovered within a week or ten days, the natives regard the disease with dread, owing to its reputation for deadliness.

In Broken Hill, Northern Rhodesia, Wallace observed 15 cases annually. The majority of victims are young adults. The onset is sudden and the early symptoms are lassitude, general dullness, and suffusion of the conjunctivæ, with pyrexia, sometimes of 103–104° F. There is tenderness over the parotids and vague pains. These are soon succeeded by widespread hæmorrhages

into the skin and mucous membranes. In natives the cutaneous hæmorrhages are most easily seen in the axilla. Bullæ are then seen on the lips, buccal mucosa, tongue, and palate, the last-named in particular. Epistaxis occurs in practically every case and subconjunctival hæmorrhages are in evidence. Bleeding occurs from the bowels as well as from the bladder. At autopsy hæmorrhagic vesicles are found in the serous membranes, the pleura, peritoneum, and diaphragm. A common finding is hæmorrhagic bronchopneumonia. Usually there are large retroperitoneal perirenal hæmorrhages. The disease is believed to be non-infectious, and there are indications that it is familial. Blackie reports involvement of the central nervous system in one of his cases. He considers that onyalai is an acute form of essential thrombocytopenia due to defective nutrition.

The diagnosis has to be made from snake-bite, in which hæmorrhagic symptoms may supervene.

Massey recommended large doses of bicarbonate of soda and cod-liver oil as the best form of treatment. Blackie found that the most efficient treatment was by blood transfusions and autohæmotherapy—by injection of 18 c.c. of donor's blood intramuscularly into the buttocks or outer aspects of the thighs.

VII. Chiufa ("Chinkumbi" and "Kanyemba")

This is a disease resembling acute gangrenous rectitis described in the earlier editions of this manual, and which has been reported from South America. Gilkes describes cases he has had under his care in Northern Rhodesia. It is found in the Luangwa and Lusenfwa valleys at an altitude of 2,000–2,500 feet. Its onset is sudden and it runs an acute course. The primary manifestation is stated to be a white powdery condition which appears round the anus and gives the appearance of "boracic acid or flour"; in women it is stated to cover the vulva as well. After a few days this disappears and the patient becomes acutely ill, with pains in back and neck and a temperature of 104° F. The anus becomes relaxed and the rectum can be seen protruding, red and angry with inflammation. Throbbing in the rectum is noted, though constipation is the rule. The inflammation travels up the large intestine until the colon is involved, when there may be diarrhœa and vomiting. In women the vagina may also be affected.

Section IX.—ANIMAL PARASITES AND ASSOCIATED DISEASES

CHAPTER XLI

PARASITES OF THE CIRCULATORY SYSTEM: BILHARZIASIS (SCHISTOSOMIASIS)

Definition.—A group of diseases caused by certain digenetic trematodes of the family Bilharziadæ which inhabit the venous system of man in various tropical and subtropical countries.

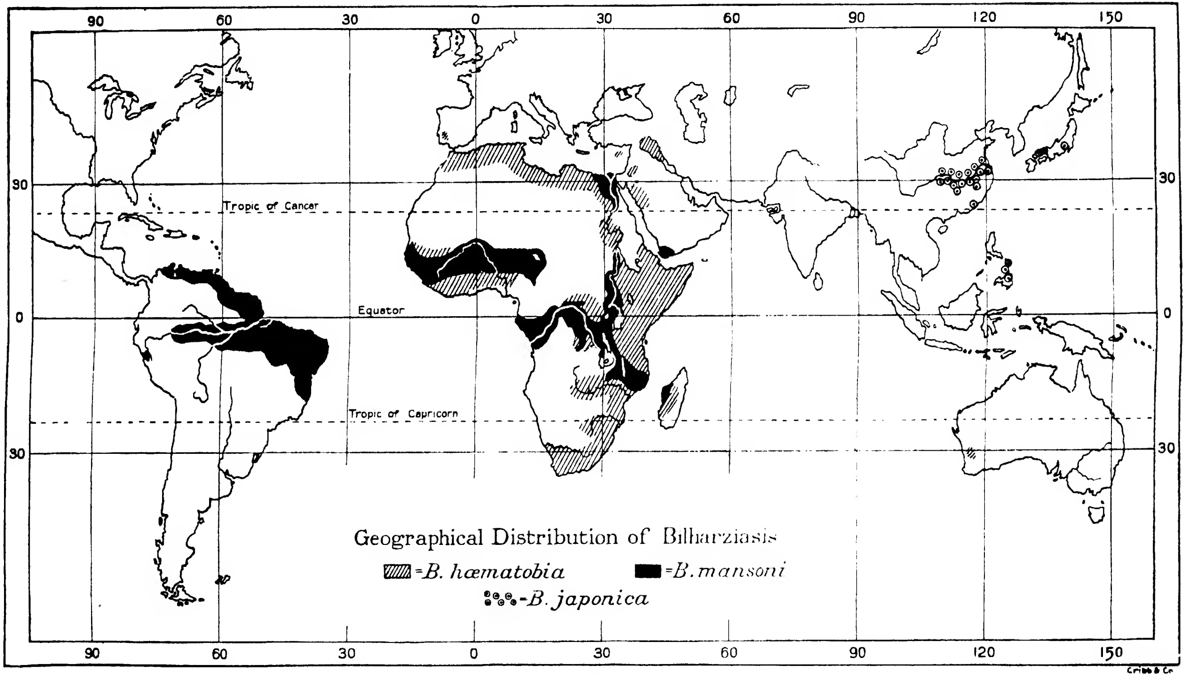
I. Genito-urinary Bilharziasis due to *Bilharzia hæmatobia*

Synonyms.—Schistosomiasis; Bilharziosis; Bilharzia Disease; Endemic Hæmaturia.

Definition.—A chronic endemic disease produced by infection of the pelvic veins, particularly those of the bladder, and occasionally those of the rectum, by *Bilharzia hæmatobia*, the eggs of which, being deposited in the mucous membrane, give rise to hæmaturia and cystitis or other symptoms connected with the urinary organs, and occasionally, when deposited in the rectum, to muco-sanguineous discharges from the bowel. The eggs of the parasite are discharged in the urine and, in certain cases, in the fæces.

History.—Hæmaturia has been known to exist in Egypt since the earliest times, and the eggs of this parasite have been found in mummies by Rüffer. Bilharz, in 1851, originally discovered the parasite, which was named *Bilharzia* by Cobbold in honour of its discoverer, but until recently it was considered that the generic term *Schistosoma* of Weinland had scientific priority.

Geographical distribution.—The eggs of this parasite were identified by Harley in Natal in 1864, and since then the disease has been found in other parts of Africa, more particularly along the eastern side of the continent, as far south as Port Elizabeth, and it is common throughout the Union of South Africa, especially in Natal. In Central Africa it occurs in the Northern Sudan, Uganda, the Congo, and Rhodesia; it is met with in West Africa as well, especially in Liberia and Sierra Leone. In North Africa it is especially common in Morocco, Algeria, Tunis and Egypt. It also occurs in Arabia, parts of Palestine near Jaffa, Iran, Iraq, Cyprus, in the town of Tavira in Portugal, in


Geographical Distribution of Bilharziasis
=B. hæmatobia
=B. mansoni
-B. japonica
Tropic of Cancer
Equator
Tropic of Capricorn
90
60
30
0
30
60
90
120
150
30
0
30
Cribb & Co.

MAP V

Mauritius, Réunion, and Madagascar. A few indigenous cases were reported, over thirty years ago, from Western Australia. (Map V.)

Precise information about the ravages of bilharziasis in Egypt are now forthcoming. Scott, as the result of 40,000 examinations, found that in the northern and eastern edge of the Delta, reaching as far as Cairo, 60 per cent. of the inhabitants are infected with *B. hæmatobia*, and an equal number with *B. mansoni*; in the apical southern half of the Delta, however, though still 60 per cent. are infected with *B. hæmatobia*, only one-tenth of that number have *B. mansoni*. The line between the first and second areas is sharp and defined, and does not correspond to any noticeable topographic, hydrographic or demographic variations. Moreover, there appears to be no difference in the number of Planorbis snails in these two regions. In the northern two-thirds of that part of the Nile Valley between Cairo and Assiut, *B. hæmatobia* infects 50 per cent. of the population, but *B. mansoni* and the Planorbis snail are absent. In the southern third, where old *basin* irrigation—that is irrigation at flood Nile only—takes the place of the new perennial irrigation, *B. hæmatobia* alone is present, but infects only 5 per cent. of the population. Heavy infection with *B. hæmatobia* is associated with perennial irrigation from high-level canals, which takes the place of flood irrigation, with alternate flushing and drying of the irrigation canals. In the district where 5 per cent. of the inhabitants are infected with *B. hæmatobia*, 1 : 1000 die from this infection; in the first-named district, the proportion rises to 1 : 22.

Ætiology. *Parasite.*—*Bilharzia hæmatobia* is a unisexual trematode. The *male* measures 1–1·5 cm. in length by 1 mm. in breadth; its cylindrical appearance is due to the infolding of the two sides of the body to form a gynæcophoric canal. The *female*, darker in colour, but 2–2·5 cm. in length, is partially enclosed in the gynæcophoric canal of the male. The parasites live in the blood of the portal vein and its mesenteric branches, but numbers dwell also in the pubic, vesical, and uterine plexuses. The longevity of this parasite is phenomenal, as it can remain active and produce viable eggs for more than thirty years.

The *eggs* are oval, and are provided at one end with a definite spine. They measure 0·16 mm. in length by 0·06 mm. in breadth. Normally they are voided in the urine, exceptionally in the fæces. It has been pointed out by Khalil that the hatching of the egg in water is due to osmotic pressure of the fluid; a 0·75-per-cent. salt solution completely inhibits the process.

Life-history.—On coming into contact with water, the eggs hatch and give rise to an active, ciliated embryo or miracidium, which, as a rule, enters a fresh-water snail belonging, usually, to the genus *Bullinus*; in the liver and hermaphrodite gland of this mollusc it develops into sporocysts, and eventually into active, bifid-tailed cercariæ which, on escaping from the snail, re-enter man by burrowing through the skin. (For further details regarding the life-history of this parasite, *see* p. 904.)

Pathology.—The character of the changes brought about by the bilharzia varies very much according to the degree and the duration of the infection. In almost every case the walls of the urinary bladder are early affected. All that may be apparent to the naked eye at this stage is a certain amount of injection of the small vessels of the mucosa vesicæ, and certain exceedingly minute vesicular or papular elevations of the surface of this membrane. When these minute elevations are examined microscopically they are found to contain eggs even in the minute blood-vessels. Later, especially in the trigone of the bladder, there are present rounded patches of inflammatory

thickening which project somewhat, are granular on the surface, and dense in consistence; on section they creak under the knife as if they contain gritty particles. It is evident that these elevated, thickened patches are the result of an inflammatory process provoked by the clusters of eggs which the microscope reveals scattered throughout their entire extent. The eggs are principally deposited in the submucosa, less extensively in the mucous membrane itself, still less abundantly in the muscular walls of the organ or in its subserous connective tissue. They tend to occur in groups, each of which is invested with a sort of connective-tissue capsule; or they may be lying in small blood-vessels which they occlude. Some eggs are seen to have undergone calcification; others are still fresh, either segmenting, or already containing a miracidium. On the surface of the rounded patches

Fig. 115.—Section of bladder-wall, showing eggs of *B. hæmatobia* in tissues.

already mentioned, phosphatic deposits, also containing eggs, are not uncommon; sometimes the patches present minute sloughs. (Fig. 115.) Besides these indurated patches, various forms of polypoid excrescence—sometimes ulcerated—may protrude from the mucous surface into the cavity of the bladder. These various hyperplasiæ frequently contain the adult parasite as well as eggs. Ferguson and others have described a nodular form of bilharziasis, an affection of the subperitoneal surface of the bladder, which closely resembles tuberculosis.

In addition to what may be designated the specific changes in the mucosa, the muscular coats of the bladder are generally hypertrophied. In consequence of this, as well as of the ingrowth of villosities and different forms of new growth, the capacity of the organ may be much diminished. Its mucous surface is generally coated with a sanguineous mucus containing

myriads of eggs. Gravel or small stones—generally phosphatic—are sometimes found either embedded in lacunæ in the hypertrophied and roughened bladder-wall, or free in the cavity. Not infrequently a similar hyperplasia occurs in the ureters, and particularly towards their lower ends, even at an early stage of this disease. In rare instances the pelvis of the kidney itself is affected. Obliteration of the ureter, both from small stones and from thickening of the mucous membrane, has sometimes been met with; this leads to dilatation of the pelvis and atrophy of the parenchyma of the kidney. It is easy to understand how, in time, these changes in the bladder and ureters may give rise to hydronephrosis, pyelitis, abscess of the kidney, and similar secondary affections. Hyperplasia of the prostate due to infiltration with eggs is sometimes found.

Hyperplasia from bilharzial infestation may also occur in the vesiculæ seminales, in the walls of the vagina, and in the cervix of the uterus, leading to corresponding bloody, egg-containing discharges.

Bilharzia eggs in small numbers have been found in the liver, in gall-stones, in the heart, and in the kidneys. The occasional occurrence of eggs in the brain, spinal cord, and lungs has already been noted. Tumours of bilharzial origin have sometimes been met with in connection with the peritoneum and ligaments of the uterus.

The eggs can be conveniently demonstrated in the tissues by digesting selected portions in 3-per-cent. potash solution.

Symptoms.—The symptoms produced by *B. hæmatobia* vary in degree within very wide limits. In the vast majority of cases the patient experiences no trouble whatever, in other instances the suffering is very great. Indirectly, from the serious nature of the lesions of the urinary organs to which it may give rise, this bilharzia is an occasional cause of death.

Early toxic symptoms, such as pyrexia with urticaria, have been noted, and may come on four weeks after exposure to infection. The *incubation period* of definite organic disease, on the other hand, varies within wide limits from three months up to two and a half years.

The most characteristic symptom of the presence of the parasite in the wall of the bladder is the passage of blood at the end of micturition, with or without a sense of urinary irritation. The quantity of blood passed and the degree of irritation are increased by exercise, by dietetic indiscretions, and by all such causes as are calculated to induce or aggravate cystitis. As a rule, it is only the last few drops of urine that contain blood; sometimes, however, the hæmorrhage is more extensive, and then the entire bulk of the urine may be blood-tinged. Occasionally, clots are passed.

If, in a case of moderate infection, the urine be passed into a glass and held up to the light, minute flocculi or coiled-up mucoid-looking threads will be seen floating about in the fluid. If it be allowed to stand, the flocculi, and perhaps minute blood-clots, will subside to the bottom of the vessel; these, on being taken up with a pipette and placed under the microscope, will be found to contain, besides blood-corpuscles and catarrhal products, large numbers of the characteristic spined eggs.

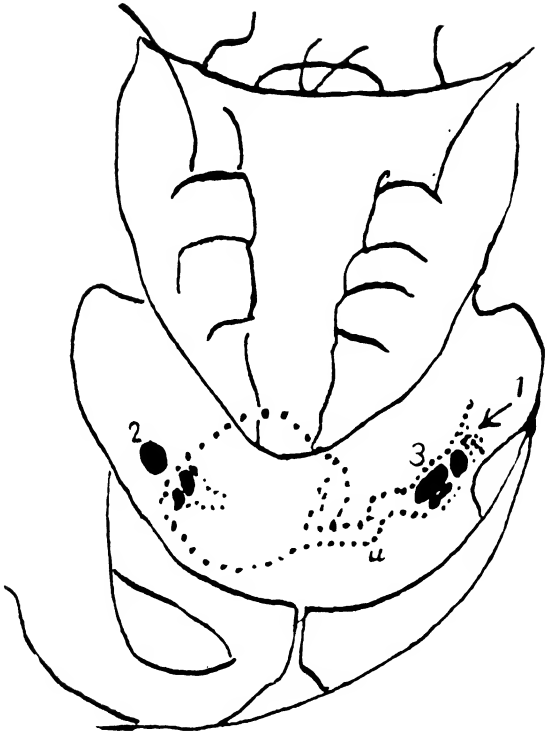
In doubtful cases, where eggs are few, the best way to find them is to get the patient to empty the bladder and to catch in a watch-glass the last few drops of urine which can be forced out by straining ; these invariably contain eggs. A low power of the microscope suffices, and is best for diagnosis.

Pain is by no means always a predominant feature ; when it occurs it generally assumes the form of a dull sense of oppression in the suprapubic region, deep-seated perineal pain, or scalding on micturition. Frequency of micturition is an early, and urgency a very common symptom. Rectal symptoms, with passage of blood and mucus, may coexist with the urinary symptoms, and a digital examination may detect ulceration above the prostatic lobes. This localized lesion may be due to *B. hæmatobia* alone, though it must be remembered that mixed infections of *B. hæmatobia* and *B. mansoni* are very common, especially in the Nile Valley. Sometimes adult worms *in copula* are passed in the urine ; this generally occurs after a copious hæmorrhage due to a ruptured vessel.

Fig. 116.—Section through nucleus of urinary calculus containing eggs of *B. hæmatobia*.

Endemic hæmaturia lasts for months or years. Spontaneous recovery is rarely complete. In ordinary cases, provided no re-infection takes place, the hæmaturia tends to decrease, although eggs may continue for years to be found in the last few drops of urine passed. In severe cases, sooner or later, signs of cystitis supervene and give rise to a great deal of suffering. Not infrequently the eggs become the nuclei for stone, and symptoms of urinary calculus are superadded. (Fig. 116.) Sometimes the pathological changes induced by the presence of the parasite in the bladder lead to the development of new growth, in which event the symptoms become more urgent and the hæmaturia perhaps excessive. Hypertrophy, contraction, and even dilatation of the bladder are not unusual. Besides the bladder symptoms there may be signs of prostatic disease, or of disease of the vesiculæ seminales, causing spermatorrhœa. In the latter case, eggs may be detected in the semen. In other instances the ureters and kidneys become involved, resulting in ureteric dilatation and hydronephrosis. (Plate XXV.) Secondary septic infection of the urinary tract with septic cystitis commonly supervenes. From the suffering attending these aggravated forms of infetion, the patients become anæmic, wasted, debilitated, and a ready prey to intercurrent disease.

Milton pointed out the extreme frequency of urinary fistula in Egypt, the result of bilharzial disease of the urethra. These fistulæ may occur anywhere in the neighbourhood of the genitals, but are especially common in the perineum and posterior surface of the scrotum, and originate from infiltration by eggs of the pubic



URINARY BILHARZIASIS.

Radiographic appearances of ureteric and vesical calculi. Note outline of bladder; u, ureteric orifice; 1, infiltrated folds of ureter; 2, calculi in ureter and in bladder; 3, papillomata and calculi.

Key to PLATE XXV

RADIOGRAPH OF URINARY BILHARZIASIS.

(By permission of Dr. G. O. Lotsy.)

PLATE XXV

(See Key, facing)

tissue or roof of the urethra just in front of the bulb, the eggs of the parasite being deposited in the mucous or submucous tissue. Stricture of the urethra is by no means uncommon from a similar cause, especially in the case of fistulæ connected with the floor of the urethra. In the male, infiltration of the penile sheath may result in an elephantoid condition with chordee and actual obstruction to the urinary flow. (Fig. 117.)

N. Makar has shown that bilharziasis of the cord and epididymis is by no means uncommon, and is determined by the anatomical peculiarities of the anastomoses between the mesenteric and internal spermatic veins, and, it may be, between the pelvic venous plexuses and deferential veins. The tunica and testes themselves are rarely affected. The onset of this disease is very gradual, and it occurs in young adults, who have their attention drawn to the swelling. The cord may be nodular and covered with lentil-like bodies, or it may be enveloped in a single big mass; the term "bilharzial rosary" well describes the condition. The employment of cytoscopy, sigmoidoscopy, X-rays and complement-fixation tests may have to be employed to arrive at a diagnosis, and to differentiate the lesions from similar ones due to filariasis, tuberculosis, syphilis, etc. In massive infiltration, the testes may have to be removed; in the early stages medical treatment is effective.

Fig. 117.—Urinary bilharziasis: pseudo-elephantiasis of penis, due to infiltration by ova. (*After Madden.*)

The majority of infections of Bilharzial disease of the spermatic cord are due to *B. hæmatobia*. The following figures are given by Makar: Infection with *B. hæmatobia* 38 per cent.; with *B. mansoni* 27 per cent.; mixed infection with *B. mansoni* and *B. hæmatobia* 35 per cent.

Bilharziasis of the prostatic urethra and seminal vesicles also occurs and is characterized by hæmospermia. Makar has reported one case of primary bilharzial disease of the gall-bladder, giving rise to duodenal stasis. The interior of the viscus was studded with sandy patches as in the urinary bladder.

Vaginitis and cervicitis have been produced by this parasite. Papillary growths and ulcers may be mistaken for carcinoma. On the vulva, papillomatous masses containing bilharzial eggs are, according to Madden, common. Similar excrescences about the anus and in the groin and perineum require microscopical examination to be distinguished from venereal warts.

Large numbers of eggs, as pointed out by Turner, may be deposited in the lungs, where they give rise to a form of interstitial pneumonia. According to Day, Shaw and Ghareeb, signs and symptoms of Ayerza's disease may be simulated. They have been found also in the brain and spinal cord, thus accounting for epileptic and paralytic symptoms from which the patients had suffered during life, but such symptoms supervene only in hyperinfected individuals. A case of bilharzial myelitis has been observed by Day and Kenawy with the customary symptoms. At autopsy the eggs of *B. hæmatobia* were demonstrated in the lumbar enlargement of the cord.

Fig. 118.—Bilharziasis of the Congo with splenomegaly. (*C. C. Chesterman.*)

Chesterman recorded districts in the Congo where the eggs of what were thought to be *B. hæmatobia* are found in the fæces only, and give rise to dysenteric symptoms closely resembling those produced by *B. mansoni*. The eggs themselves, in this instance, are longer and with more attenuated extremities than are those usually found in the urine (*see* Appendix, p. 908). Similar conditions are present in the Assiut district of Egypt, where only *B. hæmatobia* is present. (Fig. 118.)

A. C. Fisher, at the instigation of Chesterman, has now brought forward a considerable amount of evidence that this Congo disease is not due to *B. hæmatobia*, as was thought to be the case, but to *B. intercalata*, a species which in its morphology is intermediate between *B. hæmatobia* and *B. bovis*. The spindle-shaped eggs strongly resemble those of the latter species and also *B. mattheei*, with the terminal spine well developed, and may attain a length of 20 μ. The intermediary host appears to be *Physopsis africana*.

The *symptoms* produced by *B. intercalata* appear to be mild; in Yakusu (Congo) it has been found that 50 per cent. of the school-children are infected; apparently their health is not seriously affected, but sometimes the spleen and liver are enlarged. Dysenteric symptoms and abdominal pain are the only outward signs of the disease complained of, and pulmonary manifestations (in contrast to *B. hæmatobia* lesions) are practically absent. None of the toxic manifestations which usually accompany massive infections with *B. mansoni*, or *B. japonica*, have been noted. (Fig. 118.) The infected bowel, as seen by sigmoidoscopic examination, has a granular appearance suggestive of sandpaper and there are petechial patches of minute size, but no polypi or ulcers.

Bilharzial appendicitis, due to the accumulation of the eggs in the appendix, is also a clinical entity. Lovett Campbell, in northern Nigeria, found them

in 57 per cent. of all appendices removed at operation, and considers that this infection may produce symptoms requiring urgent surgical intervention. Barsoum, on the other hand, says that it does not cause or predispose to appendicitis of the ordinary inflammatory type.

Diagnosis.—The diagnosis of this disease is not difficult; the presence of eggs in the urine is decisive. (Fig. 119). In countries like Egypt, where the disease must often concur with chyluria, with stone, with vesical tumour, with gonorrhœal cystitis, and with pyelitis, as well as with prostatic disease, care must be exercised in each particular

Fig. 119.—Bilharzia hæmatobia eggs in urine, showing contained miracidia. (*Dr. H. K. Griffin, Assiut, Egypt.*)

case to separate the special factors to which the various symptoms are attributable. Thus, in chyluria concurring with bilharzial disease there will be chyle in the urine in addition to blood. In such a combination the clot which forms will be larger, will contain oil granules and globules, and very probably microfilariæ, in addition to bilharzia eggs; moreover, the microfilariæ will generally be detectable in the finger blood if looked for at night. Stone in the bladder, when suspected, has to be searched for with the sound. In gonorrhœal cystitis the history of gonorrhœa will be forthcoming. In prostatic disease enlargement of the prostate may be made out. Difficulty may sometimes arise when eggs are few in number, or when they have ceased altogether

to come away in consequence of the death of the parent worms. The mischief wrought by the parasite remains, although the eggs—the most certain evidence of the parasite's previous presence—may be discharged no longer. But, even if eggs are very few, they may still be found in the last drop or two of urine passed. If they are no longer to be found in the urine, sometimes, by scratching the surface of the bladder with a sound and examining the shreds of mucus so obtained, a few, calcified it may be, but presenting the characteristic spine, may be seen with the microscope. Further evidence may be obtained by the tests described below.

Complement-deviation.—Fairley in 1917 described a complement-deviation reaction by employing as antigen an extract of the livers of infected snails (*Planorbis boissyi*). The antigen is prepared by macerating a number of livers containing cercariæ of *B. mansoni* in absolute alcohol, filtering, and evaporating by means of a Sprengel's pump. A saline extract is then made of the dried residue and the anti-complementary dose estimated. The general technique employed is the same as for the quantitative Wassermann reaction in syphilis.

The reaction is apparently a group reaction, in so far that an antigen prepared from cercariæ of *B. mansoni* will give positive results with *B. hæmatobia* serum in 89 per cent. of early cases; further, Bettencourt and Borges have stated that a similar reaction takes place with an antigen made from *Fasciola hepatica*. A positive result may be obtained in early infections before the appearance of eggs in the dejecta. It is not so specific in the later as in the earlier stages of the disease, and may be utilized as an efficient check to treatment.

Intradermal reaction.—Fairley has also described an intradermal test, similar to the Casoni reaction in hydatid. A saline extract of dried livers, 0·5 per cent., of *Planorbis exustus* infected with *B. spindalis* is used. The extract, having been rendered bacteria-free by passage through a filter, is injected intradermally in a dose of 4 min. A positive reaction is characterized by an immediate wheal and a zone of erythema, and in from five to eighteen hours there appears a delayed type of reaction. The test is useful as a means of diagnosis in all forms of bilharziasis, but apparently persists for years after the patient has been cured.

Cystoscopic examination.—In the early stages of the localized disease (within two months of infection) the cystoscope reveals sparse grey discrete elevations in the trigone around the ureteric orifices; later, definite hæmorrhagic papules appear with surrounding inflammation. Later still, characteristic "sandy patches," resembling ridges of sea-sand, and papillomata can be distinguished. (Plate XXVI.)

Prognosis.—An important element to be considered in venturing on a prognosis is the long life of the parasite. Another important element in prognosis is the degree of infection: the greater the number of parasites, the more severe and the more extensive is the disease they produce. As with filarial infection, the greater the number of cases in a district, the greater the proportionate probability of severe

Fig. 2.

Bilharzial disease of the bladder before treatment, and one month after treatment with sodium antimony tartrate. The yellow nodules in Fig. 2 are the dead ova working their way through into the bladder cavity. They do not indicate active bilharzial disease.

(By permission of Brit. Journ. Surgery and Dr. J. B. Christopherson.)

BILHARZIASIS OF THE BLADDER.

PLATE XXVI

infections being met with. The prognosis is practically that of a chronic cystitis depending on a remediable, and not in itself fatal cause. Much suffering may often be produced, and, as a consequence, anæmia and debility. Possibly calculus may be formed; possibly grave renal disease may ensue; possibly, eventually, villous or epitheliomatous growths in the bladder. In the milder degrees of infection, which fortunately are the commonest, the patient seems to be in no way inconvenienced by the parasite, and generally escapes all serious consequences. In any case, mild or severe, there may be attacks of hæmaturia from time to time; as a rule, the quantity of blood lost is insignificant.

TREATMENT

Preliminary statement. Antimony was well known to the ancients as *stibium*, and was used by women to beautify their eyebrows: it is what Jezebel employed when she painted her face and "tired her hair." It is mentioned in the Ebers papyrus, 1500 B.C., and is recommended by Paracelsus (1480–1541). The "Parlement" of Paris in 1566 passed an enactment forbidding its use.

The organic antimony derivatives have a depressing effect on the heart, circulation, and respiration. The systemic blood-pressure falls, while the pulmonary pressure rises. Post-mortem cases of antimony-poisoning and arsenic poisoning are very similar; considerable quantities of antimony are found in the liver and spleen. After toxic doses, fatty degeneration of liver, kidneys, and heart is present, with congestion of the dura mater and cerebral vessels. According to Khalil, antimony is slowly excreted, and has a cumulative action: the principal organ of excretion is the kidney. The amount excreted in the fæces ranged from 2·3 to 4·6 per cent. of the amount injected, but the excretion of the pentavalent compounds in the urine is more rapid than of the trivalent compounds. The reactions, which are much less marked with the pentavalent than with the trivalent compounds, are cough, metallic taste, nausea, rheumatic muscular pains, vomiting, giddiness, collapse, rise of temperature, and sometimes sudden death.

The successful treatment of bilharziasis by the intravenous injection of sodium-antimony tartrate is due to Christopherson. His results have been abundantly confirmed. The drug appears to act upon the adult trematode by cumulative action, and the results of treatment are judged by observation upon the eggs in the urine. From observations made by Dye, the adult stage of the parasite is most readily affected by tartar emetic: cercariæ and miracidia are less susceptible, while the eggs are not affected to anything like the same degree.[1] For this purpose the freshly-passed urinary deposit is mingled daily with about sixty times as much warm water at 130° F., and the hatching of the eggs is observed. Under normal conditions this takes place in about five minutes, but after injections of antimony tartrate it is found that such eggs as appear in the urine are dark and shrivelled and contain dead miracidia. Christopherson, as already noted, believes this

[1] Christopherson does not agree with this statement, believing that the changes in the eggs are produced by the direct action of antimony, quite apart from any effect of the change upon the generative organs of the female bilharzia.

change to be due to the direct action of antimony upon the eggs (Fig. 120). Fairley, from experimental studies on the allied *B. spindalis* of the goat, believes that antimony acts in a selective manner upon the reproductive organs of the female bilharzia, and thus causes firstly, the shrunken appearance of the egg, and secondly, cessation of egg-laying capacity.

It should be noted that living eggs left in too long contact with *alkaline* urine fail to hatch; therefore all experiments should be performed with freshly-voided urine.

I. Tartar emetic (Sodium antimonyl tartrate).—The intravenous injections are given on alternate days over a period of four to six weeks. It is usual to begin with ½ gr. of tartar emetic dissolved in 10 c.c. of freshly-distilled and sterile water, and gradually to increase the amount by ½ gr. at a time till a maximum individual dose of 2–2½ gr. is reached. It is not always necessary to dilute to 10 c.c.: for amounts under 1 gr., 6 c.c. of distilled water are quite sufficient. Apparently, some of the toxic phenomena are avoided by dissolving the salt in 5-per-cent. glucose solution. Care should be taken not to boil antimony tartrate for any length of time or subject it to steam pressure. In injecting large numbers of patients the stock solution of tartar emetic is made up in a sterilized vaccine bottle with a rubber cap in a strength of ½ gr. to 1 c.c. of distilled water: for use this is diluted with 5 c.c. of water. The solution should be drawn into a syringe of 10 c.c. capacity, and slowly injected into the median basilic or cephalic vein. The total amount injected to kill all the trematodes should be 25–30 gr. of tartar emetic. A rapid improvement in the condition of the urine is soon observed; generally all traces of blood disappear after the injection of 15 gr. For children a total of 10 gr. appears to be sufficient, the maximum individual dose for a child being 1 gr. The course, once commenced, should be persisted in; cases almost invariably relapse if interruptions occur lasting a week or more. In Egypt (1925) the course consists of twelve injections given three times weekly till 22½ gr. of the drug have been administered, and occupies four weeks. When a small amount of diluent fluid is utilized, as suggested, only slight evidences of toxic absorption are noted, such as headache, cough, nausea and transient rheumatic pains, especially in shoulder joints.

Fig. 120.—Egg of *Bilharzia hæmatobia*, showing changes produced in contained miracidium by antimony tartrate. (*Dr. John Anderson.*)

Fairley has amply confirmed the specific action of tartar emetic on adult bilharzias. In *B. spindalis* infections of the goat, he has shown that tartar emetic in doses of 3·9 to 5·5 mg. per kilo, at daily intervals for a period of from sixteen to twenty-six days, is capable of killing off the adult bilharzia

parasites and eradicating the disease. The pentavalent compounds of antimony (Neostibosan, Neostam, etc.) do not seem to be so efficacious as the original tartar emetic. Comparative tests have shown that Neostibosan is less toxic than Neostam, but sometimes toxic skin-rashes are produced.

II. Fouadin (Neoantimosan) (Bayer).—This is a trivalent compound, antimony pyrocatechin disulphonate of sodium (containing 13 per cent. of antimony), which has been introduced since 1929, especially for the treatment of bilharziasis in Egypt. It is claimed that by this method a cure may be effected in nineteen days in place of the more prolonged tartar-emetic treatment. The drug is given *intramuscularly* in 7-per-cent. solution, and is put up in ampoules.

The dosage is as follows :

For an adult :

1st day	1·5 c.c.
2nd „	3·5
3rd	
5th	
7th	
9th	
11th	
13th	
15th	

The total number of injections should be about ten to fifteen, totalling 0·4 grm. of antimony. Of the total quantity 50 per cent. is excreted in the urine and 4 per cent. in the fæces. Late vomiting occurs in 2·5 per cent. of the cases. There is apparently no local reaction except, occasionally, spasms of coughing. The urine is examined after the last injection, and if living eggs are still present further injections are indicated. According to Khalil in 1930 some 1,474 cases were treated with fouadin and a cure was obtained in 97·6 per cent., though it is generally held by others that the results of this treatment are by no means so satisfactory as by the older methods.

Orenstein states that fouadin should never be given *intravenously*, but should be administered intramuscularly on alternate days. In more than 300 school-children treated in this manner no toxic symptoms were observed.

III. Emetine.—There is evidence that emetine also is toxic to the bilharzia (Diamantis and Erian). The injections should be given intramuscularly to children who are intolerant of antimony, or whose veins are too narrow for intravenous injections ; generally the treatment is commenced with ½-gr. doses, the maximum single dose for a child being 1 gr., while an aggregate total of 15–20 gr. may be given. Tsykalas, who has reported results in 3,800 cases, injects the drug intravenously in doses of 1½ gr. daily the total course lasting 10–14 days, and 15–17 gr. (1·12 grm.) being given. Toxic symptoms—diarrhœa, vomiting and neuritis—are apt to ensue. In his later communications Tsykalas claims that emetine is superior to every other specific. He now gives a total dosage of 1·25 grm. intramuscularly or

1 grm. intravenously. The biggest doses should be given at the commencement of the course and it should be given daily. The heart must be carefully watched and the size of the dose regulated by the body-weight. Two months should be permitted to elapse between treatments.

Fairley stated that as a result of experimental studies on *B. spindalis* of the goat, emetine given intravenously, ten to fifteen injections varying between 0·7 and 1 mg. per kilo of body-weight, causes the rapid death of the parasites, and is more efficacious than tartar emetic.

IV. Anthiomaline is recommended by Moulinard as a better drug than emetine or tartar emetic. The daily dose is 0·12 grm. and the total 1·38 grm. There are no contraindications; intramuscular injections are not painful, and there is no evidence of either local or general reactions. These lithium salts of antimony are also recommended by Cawston. Anthiomaline is very soluble and contains 16 per cent. of antimony. It is supplied in ampoules containing 2 c.c. of a 6-per-cent. solution or 0·01 grm of antimony. The doses are 0·5 c.c. for a child of twelve and 1·5 c.c. for others. The maximum dose for an adult is 4 c.c. It is best given by the intravenous route.

V. Local applications.—Stone and troublesome new growths are to be removed by operation. When distress is extreme, Mackie and others have had good results from perineal cystotomy and drainage. Perineal fistula must be dealt with on ordinary surgical principles. Hyperplasia in the vagina and cervix is best treated by scraping. If reinfection be avoided by the exercise of prudence in the matter of water, there is no need to send the patient with this disease away from the country in which the parasite was acquired.

Prophylaxis.—In the endemic districts, children, in particular, should be carefully and repeatedly warned, by school and religious teachers, against drinking or bathing in rivers, ponds, and canals. (Fig. 121.) Sportsmen should be warned against wading, especially when shooting snipe, in localities known to be infected; even fishing in fresh-water canals in countries like Egypt is not free from risk. Swamps, when slightly brackish, are safe. Drinking-water should be boiled, and every care must be exercised to prevent the diffusion of the disease by prohibiting the evacuation of excreta into or near water, where the miracidia might find the opportunity of development and transmission. This prohibition should not be restricted to patients exhibiting definite symptoms of the disease, but extended to all, because, as special inquiries have shown, a large proportion of the infected do not suffer from any troublesome symptom and are often unaware of their infection. Leiper pointed out that much might be accomplished by attacking the mollusc intermediary and the free cercaria. As regards the former, he suggested periodic drying of irrigation canals and the use of chemical manures; and as regards the latter, the use of cercariacides such as sulphate-of-soda tablets for drinking-water, and boiling, and lysol, creolin, or cresol (1 : 10,000) for bathing-water. Chlorine, in the strength (1 : 1,000,000) generally used in tropical countries to sterilize water, appears to have

no effect upon the living cercaria; the addition of larger quantities renders it unpotable.

Witenberg and Yofe have shown that chlorine is really the only agent

Fig. 121.—The intermediary hosts of *B. hæmatobia* **and** *B. mansoni* (*Planorbis boissyi* **and** *Bullinus contortus*) **in their natural surroundings.** Nat. size. (*J. K. Lund, del.*)

which can be depended upon to kill cercariæ, and that chloramine is the most effective form. Chlorine water, containing 2 grm. per litre, is prepared by introducing gaseous chlorine directly into the water; 2 grm. of ammonium chloride (NH_4Cl) are then dissolved in 100 c.c. of this chlorine water, and

the solution is left to stand for two hours at room temperature. Of this solution, 2·5 c.c. are dissolved in one litre of water. This forms the stock chloramine solution, which contains from 1–2 per million of active chloramine.

Ammonium sulphate, under experimental conditions in weak solution, kills snails in a few hours. The free cercaria lives but a short time—at most forty-eight hours—in water, but a mollusc once infected continues so for months. The free cercariæ readily pass through the ordinary municipal filter-bed, for they can traverse 30 in. of fine sand in five hours; but they perish, as has been stated, if they do not get access to an appropriate host within forty-eight hours. These facts should be taken into account by the sanitarian.

The treatment of canal water in Egypt should be undertaken in the non-irrigating season—April to July; then the canals are low and contain less than half the normal volume of water. Before treatment is commenced, the intake gate is shut and the water in the canal is reduced as low as is possible. Thus it is possible to calculate the amount of water. The length of the canal between each regulator and the width of the bed are known. The destruction of the snails is effected by adding sizolin[1] (1 : 20,000) to the water. This liquid is put up in 10-gallon drums.

The difficulty about the efficient prophylaxis of this and other forms of bilharziasis lies in the habits of the snails concerned, which reappear in pools and water-courses directly the rains recommence and after they have, to all appearances, been exterminated. Thus in Egypt Khalil states that in 1928 all Bullinus snails were completely exterminated in the isolated irrigation region of Wardan in the west of the Nile Delta, by mixing copper sulphate 1 : 200,000 in the entering water. A few months later Bullinus snails were present in large numbers, some being found on weeds caught by the pillars on a wooden bridge at the entrance of the canal. It therefore seems as if all the canals in the Delta were restocked from the Nile. That infected snails are found in the Nile itself, there appears to be little doubt, for 25 per cent. of the children who have never left Roda Island (which lies opposite Cairo) are infected with *B. hæmatobia*. In 1919 the Editor summed up the situation in Egypt as follows:

> "During the spring months of the year the sluice gates are open and the Nile water is coursing through the canals of Lower Egypt, bearing with it large masses of fresh-water weed and other vegetation, and it is to these that most of the infected snails are to be found clinging."

An organized attempt is being made in Egypt, by educational means in schools, by pamphlets, and by diagrams, effectively to deal with the problem. The efforts of the sanitary authorities have received the backing of the religious authorities, but the difficulties are very

[1] Manufactured by the Standard Disinfectant Co., 43, Gower Street, W.C.1

great and progress must necessarily be slow. These remarks are applicable to *mansoni* as well as *hœmatobia* infections. Under the direction of the Under-Secretary of State for Public Health in Egypt, there are fifty-six units engaged in anti-bilharzia work, prophylaxis being mostly upon the therapeutic basis.

A novel suggestion for the practical prophylaxis of bilharziasis has been put forward by Archibald in the use of the fruit of *Balanites œgyptiaca*. a tree which grows naturally in the irrigated areas of Africa, Arabia, Egypt, and Palestine. Prophylactic measures suitable for one area are unsuitable for another, and the Arabs resent chemical treatment of their only potable water. In *Balanites œgyptiaca* a suitable prophylactic tree has been found. It fruits prolifically for six months annually ; its date-like fruit is eaten, but the berries, kernels, bark, roots and branches contain an active principle which is deadly to molluscs, miracidia, cercariæ, tadpoles, and fish. For actual use the berry is advised : one weighing 5·2 grm. suffices to kill bilharzial molluscs when soaked in 30 litres of water. Thirty-five berries are added to a 4½-gallons petrol-tin of water and stood overnight. The next morning the softened pulp is crushed in water and stood for twenty-four hours, and this suspension is added to a cubic metre of water. This suspension may be obtained naturally if there is a dense afforestation of the borders of canals and pools which harbour bilharzia snails.

II. Bilharziasis due to *Bilharzia mansoni*

Definition.—A chronic endemic disease caused by *Bilharzia mansoni*, giving rise to dysenteric and other symptoms referable to the intestinal canal, and characterized by the eggs of the parasite in the fæces. In the early stages there may be general symptoms, such as fever and urticaria, indicating absorption of the toxins excreted by the adult parasites. One of the visceral manifestations of this infection is Egyptian splenomegaly, a common disease in Egypt and Northern Nyasaland, which in many respects resembles kala-azar, especially the infantile variety.

History and geographical distribution.—The occurrence of a bilharzia producing lateral-spined eggs was noticed by Bilharz in 1851, but he confounded it with *B. hœmatobia ;* subsequently several observers encountered female worms with lateral-spined eggs in utero, and the idea of a distinct species suggested itself to Sonsino and others ; but this idea was at once discarded for other hypotheses—for instance, that the peculiar position of the spine was due to distortion of the egg-shell in passing through the muscular coat of the rectum.

Manson, in 1903, found numerous lateral-spined eggs in the fæces of a patient from Antigua who had never suffered from hæmaturia. The peculiarities of the case led him to think that the lateral-spined egg indicated a new species of bilharzia. In 1907 Sambon, on comparing specimens of the type characterized by lateral-spined egg with *B. hœmatobia* and other bilharzias, and taking into consideration its peculiar geographical distribution and distinct pathogeny, proposed that it should be considered a distinct species—*Bilharzia mansoni*. He subsequently described many cases of lateral-spined bilharziasis from South America. Holcomb and da Silva first

described the peculiar anatomical distinctions of *B. mansoni*, but the duality of species was finally settled by Leiper in 1916. He proved that the miracidia, hatching from lateral-spined eggs, after developing in snails of the genus *Planorbis*, developed into adults with constant morphological distinctions. Subsequently this was confirmed by Fairley and the Editor in Egypt, and by Lutz in Brazil.

Possibly this bilharzia is originally a West African species, imported into the New World by African negroes. Its geographical distribution, as far as is known at the present day, extends from the Nile Valley throughout Central and West Africa, the West Indies, and South America ; most probably its range of distribution is limited by that of an appropriate intermediary host of the genus *Planorbis*. (Map V.)

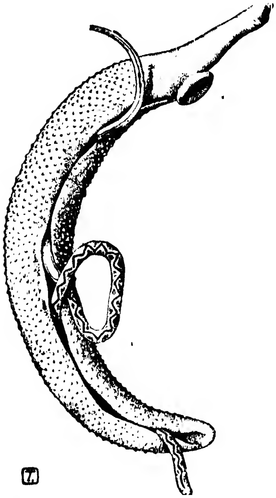


Fig. 122. — *Bilharzia mansoni*, male and female. × 8. (*Partly after Looss.*)

Epidemiology and endemiology. — Apparently *Bilharzia mansoni* requires slightly different conditions for its propagation than does *B. hæmatobia*, so that, though frequently found associated in Africa, yet there are areas in the Southern Sudan and in West Africa where *B. mansoni* infection is found and *B. hæmatobia* not at all. Although bilharziasis occurs in eleven out of fourteen provinces in the Sudan, *B. hæmatobia* is the common type in the north, and south of the Upper Nile Province intestinal bilharziasis is the only type. (Map V.)

Infection is acquired during the months of the year when water is sufficiently shallow to permit of a high concentration of cercariæ. In the case of inland lakes the seasonal incidence is from October to the end of January, but in the Nile backwaters, the danger period is usually February to June.

Ætiology.—The parasite much resembles *B. hæmatobia*. The distinguishing features are that it is generally smaller in size and more grossly tuberculated. There are other minor points (Fig. 122). The female deposits one or two eggs at a time—a circumstance perhaps explicable by the peculiar structure of the uterus. The eggs are somewhat spindle-shaped, are provided with a lateral spine (Plate XXXIII, 12, facing p. 1025) and are generally slightly shorter than those of *B. hæmatobia*, 0·15 mm. in length by 0·06 mm. in diameter. These eggs are passed out in the fæces, rarely in the urine, and hatch out a ciliated miracidium. (*See also* p. 909.)

Pathology.—The eggs of *B. mansoni* may be found in great numbers in the liver, where they give rise to a peculiar form of " pipe-stem " cirrhosis. Sandy patches, due to effete calcified eggs, cover large areas of the intestinal surface, and may give rise to acute choleraic diarrhœa. Deposits of black pigment granules take place in the interstitial and secreting cells of the liver,

and have been shown to occur in both *B. mansoni* and *B. hæmatobia* infections, but to be commoner and more abundant in the former. It is golden brown or sepia in colour, and gives the same reactions as malarial pigment (hæmozoin). The lymph-glands in the latter situation and in the retro-peritoneal tissue are enlarged. There is generally an appreciable hypertrophy of the spleen, which may possibly be attributable to toxic absorption and gives rise to the clinical state known as Egyptian splenomegaly.

The affections of the colon may be classified into four types—(*a*) those with simple thickening of the mucous membrane ; (*b*) thickening of the mucosa with papilloma-formation ; (*c*) pericolic tumours associated with papillomata ; (*d*) polypi of the cæcum which may lead to intussusception.

The small intestine is hardly ever affected, except in its lower part. In the colon the disease causes the formation of septic foci, and ulceration of the bowel-wall appears to be produced by the tearing-off of pedunculated papillomata by the peristaltic action of the intestine. By this means, and by sloughing at the base, clear-cut ulcers are produced which may become subsequently infected with *Entamœba histolytica*. Perforation of the bowel may occur. Fairley and Lampe have drawn attention to the similarity of the disseminated pericolic nodules to miliary tuberculosis and also to infiltration of the mesenteric glands by bilharzia eggs resembling that disease.

Shaw and Ghareeb have emphasized the importance of pulmonary damage as the cause of death in *B. mansoni* as well as in *B. hæmatobia* infections. The main damage is due to embolism by eggs derived from female flukes outside the lung. They are filtered out in the arterioles which accompany the bronchioles, producing diffuse arterial changes or Ayerza's disease. Parenchymatous tubercles are found containing the characteristic eggs. In some 10 per cent. of cases, the adult worms have been found in the pulmonary arteries.

Visceral Bilharziasis (due to *B. mansoni*) ; Hepato-lienal Fibrosis ; Egyptian Splenomegaly

Splenomegaly associated with cirrhosis of the liver is common in all parts of Upper and Lower Egypt, where 20 per cent. of infants under four years of age are found to have splenic enlargement and anæmia. It is common among the working class at all ages up to thirty ; in the young it is apt to run a severe course, while at a later age the chronic form, progressing to ascites, is met with. In children the disease is generally associated with rickets : in adults, with ancylostomiasis. A similar disease has been recorded by Dye from Northern Nyasaland in patients infected with *Bilharzia mansoni*. Day came to the conclusion that in Egypt this disease is a peculiar manifestation of *B. mansoni* infection. He regarded it as distinct from Banti's disease in that the hepatic changes are noted from the commencement, while the eosinophilia and recurrent fever disappear under specific treatment with tartar emetic. The hyperplasia of the spleen appears to be secondary to the hepatic cirrhosis, and to the pathological condition of this organ are to be ascribed the anæmia and leucopenia which are found in advanced cases of the disease. The patients with advanced cirrhosis are just those who have few intestinal symptoms, and who pass scanty, or it may be, no eggs in the stools. Eggs of *B. mansoni*

may be found on digestion of solid organs, such as the liver and spleen, with potash.

Pathology of Egyptian splenomegaly.—Ferguson noted that the average weight of the spleen is 30 oz.; it may reach 300 oz., and, according to Day, may contain a few eggs of *B. mansoni.* It is firm in consistence; microscopically there is a general hyperplasia with active phagocytosis of the red cells by macrophages.

Onsy states that the only certain method of finding eggs in these enlarged spleens is by macerating the tissues in 20-per-cent. soda solution and subsequent centrifugation. The eggs are phagocytosed by giant cells, a process accompanied by considerable eosinophilia. On the other hand, in order to account for the widespread nature of the visceral lesions and the paucity of eggs, the view has been put forward by Girges and others that Egyptian splenomegaly is caused by infection by male parasites of *Bilharzia mansoni,* without the presence of the female; but this view is not widely held.

Fig. 123. — Rectal bilharziasis: adenomata prolapsed through anus. (*After Madden.*)

Abdel Shafi asserts that although the incidence of eggs in the liver is fairly high, yet other organs and tissues show much heavier deposits of them, that an infection of the liver alone is unknown, and that the number of eggs in the liver substance is small in comparison to the extensive cirrhotic changes in that organ.

The liver is usually enlarged in the early stages, and presents the picture of early multilobular cirrhosis with isolated necrotic foci. In the more advanced stages the organ is shrunken and firmly fixed to the diaphragm by adhesions. There is a comparative absence of bile-duct formation. The bone-marrow shows no great disturbance of the hæmopoietic system.

Symptoms of intestinal bilharziasis.—*B. mansoni* inhabits chiefly the branches of the portal vein in the liver, and the mesenteric veins. Its eggs, deposited within the submucous layer of the rectum, give rise to dysenteric-like symptoms, commencing six to eight weeks after infection; mucus with blood is passed from time to time, the egg-laden stools becoming frequent and their passage being perhaps attended with tenesmus. In certain well-established cases small (sometimes large) branching, soft growths are to be felt inside the sphincter ani. They resemble polypoid growths and are apt to be mistaken for piles. They may extend as high up the bowel as the sigmoid flexure. On tearing up one of these growths one can see the eggs in the debris. (Fig. 123.)

In mass infections, in early cases, toxic symptoms resembling those of katayama disease (p. 739) are noted, especially in Europeans. The general symptoms consist of a remittent pyrexia, with urticaria, marked abdominal pain, anorexia, rigors, and pulmonary symptoms. (Chart 26.) Pons states that cough is invariably present in early cases, and tenderness is found over the liver, spleen, and intestines, being especially marked over the cæcum. On abdominal examination of these dysenteriform cases, there is frequently found a co-existing enlargement of the liver as well as of the spleen. A pronounced leucocytosis with a high eosinophilia (up to 76 per cent.) has been reported.

Later, localized symptoms with passage of dysenteric motions supervene.

In the terminal stages of the disease large abdominal tumours may form, easily palpable, and actual intestinal stasis or distension may take place. Infiltration of the buttocks with eggs, leading to induration and fistulæ, is not uncommon. When the liver has become markedly cirrhotic, ascites may be present. Pneumonia from egg deposition in the lungs is an occasional complication.

Sometimes the dysenteric attacks may develop into acute diarrhœa of a choleraic type, which may prove fatal. Deposition of the eggs of the parasite in the appendix occurs comparatively commonly and produces symptoms of a subacute appendicitis. Generally the organ is much thickened and infiltrated so that it can easily be palpated. The diagnosis of bilharzial appendicitis from septic appendicitis and that of amœbic origin becomes a trite question.

Symptoms of the hepato-lienal form (Egyptian splenomegaly).—The symptoms of this condition, which has been termed "Egyptian splenomegaly," appear to be more objective than subjective. There are irregular fever, wasting,

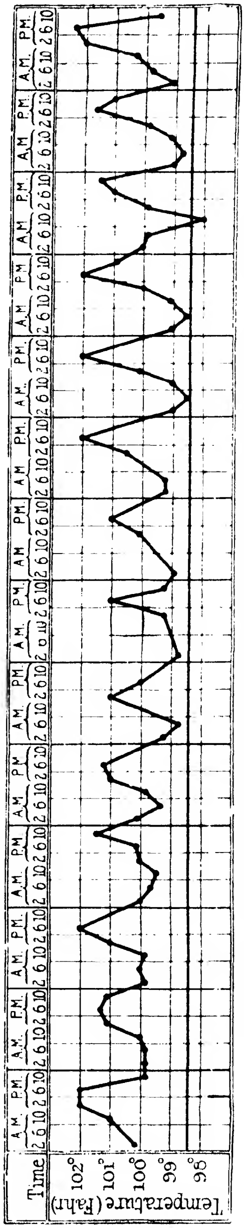


Chart 26.—Four-hourly temperature chart of acute bilharziasis (*B. mansoni*). (*Lawton.*)

and a striking pallor. The spleen is obviously enlarged, hard, and firm, often reaching to the umbilicus (Fig. 124); the liver also in the early stages is enlarged. Vomiting and diarrhœa are frequent. In the later stages œdemas of varying degree and purpuric rashes may ensue. The fever is generally irregular in type, intermittent, and not amenable to quinine. The splenic enlargement causes pain and discomfort, especially after meals, and on exertion gives rise to a dragging sensation, though the symptoms are caused by debility and anæmia. As the disease progresses, so the pyrexia increases, till the steady enlargement of the liver and spleen causes the costal angle to expand. Hæmatemesis often occurs, but jaundice is rare. The final stage is ushered in by cirrhotic changes in the liver, which becomes hard and firm, and shrinks within the costal margin. The spleen also becomes fibrotic, but does not proportionately decrease in size. The pain, which is due to perisplenitis and perihepatic adhesions, increases, while vomiting is a common feature. Finally, the patient succumbs with all the symptoms of hepatic cirrhosis, ascites, and emaciation. Death is usually due to pulmonary complications.

Fig. 124. — Egyptian splenomegaly. (*After Richards and Day; by permission of "Brit. Journ. Surg."*)

Kenawy has described a continuous venous hum which may be heard by the stethoscope over the liver, and which he considers is characteristic. The hum becomes louder during inspiration, and also in the standing position. Subsequent to splenectomy the sound disappears, and is probably due to the removal of some venous communication. Unfortunately this sign is of no great assistance in differential diagnosis, for a similar phenomenon has been noted in other forms of cirrhosis, as well as in Banti's disease.

The blood picture varies at different stages of the disease. In the early stages there is a distinct leucocytosis of 17,000, and myelocytes may be present; later a progressive anæmia of the chlorotic type becomes apparent, with a leucopenia of 3,000 and a mononuclear increase of 10–17 per cent.

Among the rare complications, thrombosis of the portal vein and hepatic carcinoma have been recorded.

The course of the disease is generally protracted : in older children and adults it may run twenty years or more. Ascites is always regarded as an unfavourable symptom. In all its aspects this stage of the disease resembles the analogous bilharziasis japonica.

Diagnosis.—The characteristic eggs are easily found in the fæces under a low power of the microscope; they may be very scanty, and it is necessary to examine three or more specimens before arriving at a negative diagnosis. (Fig. 125.) They are more easily found in solid than in fluid motions, especially in the outer portions of a scybalum. Quite a high proportion of cases are latent—that is to say, they do

Fig. 125. Photomicro. of miracidium of *Bilharzia mansoni* escaping from egg. × 1,500. (*Dr. A. J. Chalmers.*)

not present any of the more urgent symptoms. The Editor has found the examination of mucus and scrapings from the rectal mucosa obtained through a proctoscope or sigmoidoscope to be more reliable than a fæces examination. Allen Scott also considers that the highest efficiency is obtained by means of rectal swabs. On examination of over 1,000 fæcal specimens by three different techniques and by a combination of them, *viz.*, egg-counting by Stoll-Hausheer method, using 0·005 c.c. of fæces diluted in decinormal soda; sedimentation in normal saline (constituting a concentrated egg-count), he found that the swab method gave the best results. In about 5 per cent. of cases in Egypt the characteristic eggs may be found in the urine as well as in the fæces.

In this form of bilharziasis the total serum proteins do not vary much from normal, but the globulin and the globulin-albumin rates and the percentage of euglobulin are increased, and they are still further increased in patients with splenomegaly (Khalil and Hassan). The formaldehyde-test may, therefore, not always be reliable in differentiation from leishmaniasis.

Fülleborn recommended the Telemann method of finding the eggs when scanty in the fæces: the fæces are shaken up with a mixture of concentrated hydrochloric acid 1 part, water 1 part, ether 2 parts, and strained through gauze; the filtrate is centrifuged and examined. The fæces may be mixed with water and the eggs encouraged to hatch, when the miracidia are more easily detected (Appendix, p. 1031).

The complement-deviation reaction is the same as in *B. hæmatobia* infections (p. 722).

In rectal disease, should *B. mansoni* be suspected, one of the adenomatous growths may be removed by means of forceps and examined for eggs.

Sigmoidoscopic examination may reveal a pedunculated adeno-papillomatous growth in the upper part of the rectum, but usually this is unnecessary, as the growth can be felt by digital examination and may be seen protruding in polypoid masses from the anus. In very early cases merely granular patches can be detected on the rectal mucosa from which eggs may be obtained by scraping with an instrument through the sigmoidoscope. The localized thickening of the large intestine, due to polypi and pericolic growths, can be palpated in heavily infected subjects through the abdominal wall. They are most often situated in the transverse and pelvic colon.

The differential diagnosis of the hepato-lienal form has to be made from Banti's disease and other forms of splenomegaly. It has been pointed out that a ready method is to hand in adrenalin, which on injection lessens the size of the spleen in the former disease.

Treatment

I. Antimony treatment.—Gross changes in the organs are more extensive than in *B. hæmatobia* infections, due partly to toxic absorption and partly to deposition of eggs, and it is possible, as Madden and Day have reported from Egypt, for the adult worms to be killed by tartar-emetic treatment but for the effects of their presence to remain. Hence it may prove necessary to operate upon polypoid or adenomatous growths obstructing the intestinal lumen. In early cases antimony is as successful as it is in cases of *B. hæmatobia*. Lampe in Surinam treated out-patients with three injections of 3 c.c., 5 c.c. and 7·5 c.c. of a 1-per-cent. solution of tartar emetic thrice weekly, with a total of 150–200 c.c., the whole course occupying six to seven weeks. Dye and others have tried rectal injections of tartar emetic as being especially applicable to small children, who can take 16 gr. by the rectum without toxic effects, but the amount of the drug ab-

sorbed by this method is unknown. Five to seven daily injections are necessary.

The Editor is definitely of the opinion that *B. mansoni* is more difficult to kill off than *B. hæmatobia,* and requires larger doses of intravenous tartar emetic—up to a total of 50 gr. As in *B. hæmatobia* infections, fouadin is extensively employed as an intramuscular injection, especially in Egypt, but it does not appear to be as efficacious. Khalil has reported that a few cases of sudden death have occurred. From Egyptian statistics in 1934, it is learned that the total number of bilharzia cases which received nine or more injections of fouadin were 1,938 : of these 53 per cent. were cured, 21 per cent. required eleven injections, and the remainder required even more. After thirteen injections, signs of drug intolerance were noted. (*See* p. 725.)

Khalil considers that there are individual variations in the excretion of fouadin, idiosyncrasies to this drug being met with. The rate of renal excretion is most important, and the drug is, therefore, most easily tolerated by children. Any degree of kidney damage is a contra-indication to its use. Usually, after the fifth injection only dead eggs of *B. mansoni* can be found in the fæces. Relapses are recorded in 33 per cent. of cases. Fouadin gives a positive catechol test in the urine—that is a green colour with ferric trichloride which changes to violet on adding sodium carbonate. If the urine is not clear, it must be centrifuged. As in *B. hæmatobia* infections, *anthiomaline* injections are now being employed (p. 726).

II. Emetine treatment.—Apparently emetine is as efficacious in this disease as it is in *B. hæmatobia* infections. The amount necessary, according to Maciel, is about 0·6 grm. (9·2 gr.) in a series of ten injections. The initial two injections should be ½ gr. each, the remainder 1 gr. Emetine should be reserved for those patients who are intolerant of tartar emetic.

III. Operative treatment.—Dolbey and Fahmy held that the only rational method of obtaining a permanent cure in cases with extensive disease of the rectum is to excise the whole tube of mucous membrane. Lengths of 12–15 in. can be removed with ease. A circular incision is made at the junction of skin and anal mucous membrane ; the external sphincter and levator ani attachment are separated by blunt dissection : when once the latter has been separated, the mucous tube may be loosened by the gloved finger and withdrawn until the upper limit of the papillomata is reached. Recovery is uneventful ; there is little tendency to retraction of the tube, and control of the anal sphincter is regained. This operation is unsuitable for very anæmic or debilitated patients.

IV. Operative treatment for the hepato-lienal form.—According to Richards, in cases with ascites, palliative operative interference, such as frequent tapping and the Talma-Morrison operation (omentopexy), is permissible. In early cases, before the development of ascites, he performed splenectomy with success. Coleman, Bateman

and Stiven have since confirmed the value of this operation. The mortality-rate is about 15 per cent. and deaths are due to late shock. Great care is still necessary in the selection and preparation of cases for operation. Ascites, pellagra, heart disease and debility are contraindications. A considerable leucocytosis should be considered a bar to operation, and it is necessary to differentiate the condition from leukæmia. An injection of pneumococcal vaccine should be given the night before the operation to prevent the development of this complication. In his recent account of 390 cases, Stiven states that five to six weeks' treatment preliminary to operation is necessary. Preliminary treatment should consist of carbon tetrachloride to get rid of intestinal parasites and intravenous injections of neo-salvarsan for syphilis. The weight of the spleens removed by this surgeon averaged $3\frac{3}{4}$ lb. The favourable effects appear to be permanent, and ascites does not develop. Day claims that early cases are curable with tartar emetic.

Stiven operates with spinal anæsthesia with stovaine, making an incision, varying in length with the size of the spleen, down the centre of the left rectus parallel with the middle line, and starting at the costal margin. Skin and rectal sheath only are divided by the knife, the rectus itself being separated into two equal parts by a sweeping action of the finger. The peritoneum being opened, in the absence of adhesions, the spleen can be delivered through the wound. The pedicle is clamped and the organ removed. The former is now transfixed with a long pedicle needle armed with black and white linen thread, linen being less apt to slip than the silk, and the difference in colour insuring recognition of the necessary interlocking. After operation patients are given nothing to drink for twelve hours and then strict diet for five days. Subsequently a purge is administered. Nourishing diet and iron and arsenic are given. Patients usually leave hospital after fifteen days.

Prognosis.—This is the same as for *B. hæmatobia*, but it must be remembered that the disease generally assumes a latent form, and that even large intestinal polypi may give rise to little or no inconvenience.

Cases with papillomata of the rectum, dysenteric symptoms, tenesmus, and anæmia, and those with actual obstruction of the intestinal canal and cirrhotic changes in the liver, must be regarded as serious.

Prophylaxis is the same as in *B. hæmatobia* (p. 726). There appears to be a greater probability of contracting the disease in the neighbourhood of canals that are the favourite haunt of *Planorbis*, of which a high proportion (50 per cent. or more in some cases) are found to be infected with the cercariæ of this trematode in Egypt. In northern Nigeria and in Kenya, however, cases of infection have been recorded from bathing in clear limpid pools containing no obvious aquatic vegetation.

III. Eastern Bilharziasis due to *Bilharzia japonica.*

Synonym.—Katayama Disease.

Definition.—A chronic endemic disease of Eastern Asiatic countries, caused by *Bilharzia japonica*, and characterized by great enlargement of the liver and spleen and the development of ascites. The eggs of the parasite are discharged in the fæces. Initial toxic symptoms, urticaria and pyrexia, are commonly observed.

History and geographical distribution.—For very many years an endemic disease characterized by splenomegaly, enlargement of the liver, cachexia, ascites, pyrexia, and dysenteric symptoms had been observed. In 1888 Majima found eggs in a cirrhotic liver, and in 1904 Katsurada saw a miracidium emerge from similar eggs which he had found in fæces; later he discovered the adult trematode, *B. japonica*, in the portal veins of the cat. In that year Catto noted similar parasites at the autopsy of a Chinaman in Singapore. The next addition to our knowledge was made by Katsurada, who succeeded in communicating the parasite to cats by immersing their legs in the water of certain ponds reputed to convey the disease. In 1913 Miyairi and Suzuki traced the parasite, through a snail common in the infected districts, back to the vertebrate host: an observation confirmed in the following year by Leiper and Atkinson.

So far, the parasite has been found principally in Chinese and Japanese, though a few Europeans—mostly naval officers and sportsmen, addicted to snipe-shooting in the rice-fields—have acquired the disease. Its present range, as far as is known, may be stated as follows: In China it occurs in endemic foci in the Yangtse basin, from Ichang, 350 miles above Hankow, to the sea; in the provinces of Hunan (Siang River) Hupeh, Anhwei, Kiangsu, and Kiangsi. An endemic centre has recently been reported from Shiuchow, on the North River near Canton, and also from Foochow (Fukien). It has been recorded on the Burmese border between Yunnan and the Northern Shan States. In Japan it is especially prevalent in the province of Hiroshima and in the village of Katayama. Endemic foci also exist in Southern Formosa, and in the Southern Philippine Islands—Samar, Leyte, and Mindanao. (Map V.) In countries where it exists, dogs, cats, rats, and imported cattle are found naturally infected: native cows, on the other hand, appear to be immune.

Ætiology.—The *parasite* closely resembles *B. hæmatobia*, though it is smaller and the integument is smooth and non-tuberculated. In proportion, the acetabulum or ventral sucker is longer and stouter than in either *B. hæmatobia* or *B. mansoni*. The *eggs*, smooth and slightly oval, measure 0·08 mm. by 0·06 mm., and pass through the intestines into the fæces. They possess a rudimentary lateral spine, and show considerable variation in size, but in the uterus of the female bilharzia they are much smaller. (*See* p. 912.)

The miracidium, after casting its cilia, develops in fresh-water molluscs of the genus *Oncomelania*[1], Gredler, 1881, which has a widespread distribution in Japan and China; probably all species of this genus are potential carriers of *B. japonica*.

Pathology.—The outstanding feature is the great enlargement of the liver and spleen. The former is hypertrophied and nodular, from the formation and contraction of fibrous tissue; on digesting with 3-per-cent. potash

[1] There has been much confusion as to the correct nomenclature of these snails; the reader is referred to Appendix, p. 914.

solution, it is found to contain many eggs. The great enlargement of the spleen, on the other hand, is probably due to absorption of toxins or, possibly, to back-pressure, as eggs are seldom found in this organ. As in other forms of bilharziasis, granules of black pigment are found in both viscera. The appendices epiploicæ are greatly thickened and may be matted together; the mesenteric and retroperitoneal lymph-glands are enlarged; hypertrophy and thickening of the lower parts of the intestinal tract, with formation of ulcers and polypoid growths filled with eggs, are generally noted. The bladder is unaffected.

Occasionally, indurations of the pia mater and granulomatous lesions of the cerebral cortex have been found, in which the eggs of the parasite are present in great numbers. The young forms of the parasite enter the general circulation through the veins and collect in the lungs, and apparently enter the liver by traversing the mediastinum and the diaphragm. Inside the portal system they soon reach maturity. Infection of the fœtus during intrauterine life is apparently possible.

Symptoms.—The disease produced by *B. japonica* is a serious one and, when pronounced, sooner or later proves fatal. The gravity of any given case will depend, amongst other things, on the degree of infection and the circumstances of the patient. Of 1,077 persons near Shushima, Japan, examined by Koiki, 42 were found infected. Of these 42, only 22 were not in good health. Penetration of the skin by the cercariæ causes an intense pruritus, partly mechanical, and partly due to an irritating substance secreted by the larvæ. The erythema thus produced was formerly regarded by the Japanese as a skin disease, "kabure." The same happens after infection with the cercariæ of the other two human bilharzias—*B. mansoni* and *B. hœmatobia.*

The course of the disease can be divided into three stages. The *first* (Katayama disease) occurs shortly after infection and lasts about a month. It is associated with toxic symptoms—pyrexia, urticaria, abdominal pain, paroxysmal cough, a leucocytosis, and a high eosinophilia (60 per cent. or more). Dermatographia is common. The *second* stage is characterized by great emaciation and is accompanied by dysenteric symptoms and enlargement of the liver and spleen. The *third* or final stage, when it does supervene, occurs from three to five years after infection. In this the liver and spleen are cirrhotic and enlarged (hepato-lienal fibrosis). Ascites and œdema of the extremities appear, with anæmia and exacerbations of the dysenteric symptoms (Fig. 126). The patient may die of exhaustion or of some terminal infection. Jacksonian fits, hemiplegia, and even total blindness owing to deposition of eggs in the central cortex, and destruction of the visual centres, have been described.

Diagnosis.—All cases of urticarial fever from the endemic districts should be watched for many months (especially if eosinophilia persists after the subsidence of the primary attack) and the stools examined for eggs of *B. japonica.* All cases of chronic intestinal disturbance,

especially if associated with enlargement of liver and spleen, from the districts mentioned should be regarded as possible cases of bilharziasis, and the blood and stools should be examined. If the characteristic eggs (Fig. 127) are discovered the diagnosis is established.

A complement-deviation reaction, as in *B. hæmatobia*, with antigen made from cercariæ, may be employed ; and a similar reaction results with extracts from the bodies of the adult trematodes when the serum of an artificially-infected horse is employed (Suezasu, 1917). According to Faust and Meleney, the aldehyde or serum-globulin test is strongly positive in many cases.

It is said that ferments are given off by the body of the trematode, one of which is allied to trypsin, and digests albumin in an alkaline medium.

The disease in its terminal stage has to be differentiated from Banti's disease and from kala-azar. Campbell states that most cases of Banti's disease in the Far East are in fact bilharziasis japonica. Louchs has suggested that a safe method of making a positive diagnosis is by biopsy of the liver during the operation of splenectomy and the demonstration of the eggs, when they are not apparent in the fæces. The differential diagnosis has to be made also from Jacksonian epilepsy and tumours of the brain, since deposition of the eggs in the cerebral cortex may give rise to granulomata of considerable size.

Fig. 126.—Asiatic bilharziasis. (*Photo : Dr. J. A. Thomson ; courtesy of Wellcome Bur. Sci. Res.*)

Treatment. — Antimony tartrate, given in the same doses and in the same manner as for *B. hæmatobia*, appears to be equally efficacious in killing off the adult trematodes. A total amount of 24 gr. or more is necessary. In two cases under the care of the Editor, Jacksonian fits disappeared after treatment. According to Faust and Meleney, 22–30 gr. of intravenous tartar emetic over a period of eighteen to twenty days is usually curative. Kastein and others have reported that intramuscular injections of fouadin as in *B. hæmatobia* infections up to 5 c.c. doses are effective.

Unfortunately, in China and Japan patients only apply for treatment when in the advanced stages of the disease ; in these the

intestinal ulceration and the hepatic cirrhosis are generally so pronounced that this treatment is of little avail.

As in Egyptian splenomegaly (p. 737) splenectomy has been employed, but so far with little success, the hepatic cirrhosis being usually too far advanced. It has been advocated by Campbell that, if the blood-platelet count rises after the delivery of the spleen during the operation, the splenic artery should be tied, and the spleen returned into the abdominal cavity.

Emetine.—Probably injections of *emetine hydrochloride* are as efficacious as in the other bilharzia infections; but it is necessary to remember that, as has been shown experimentally in goats infected with *Bilharzia spindalis*, fatal verminous thrombosis of the pancreatic and portal veins, as the result of the presence of dead parasites, may occur.

Fig. 127. -Eggs of *B. japonica* in fæces. × 250. (*Photomicro Dr. J. Bell.*)

Prophylaxis.—Water reported to cause the disease should be boiled, or avoided, for drinking or bathing purposes. Sportsmen, if they must wade in such waters, should wear long boots or waders. According to Narabayashi, lime in a solution of 1 : 1000 is the most economical reagent for the extermination of the intermediary host (*Onchomelania*), and kills the cercariæ in thirty minutes. It is especially recommended because of its value as a fertilizer. It is said that the eggs remain viable for ten days outside the body in a solid motion, and this factor should be recognized in formulating sanitary measures. Specific treatment in out-patient clinics will help to eliminate carriers of the disease, whilst educational propaganda, especially in China, is all-important. The prophylaxis of this form of bilharziasis presents many difficulties, for the disease attacks domestic animals, especially dogs, as well as man. The snail vectors, moreover, live in almost inaccessible situations, but it has been shown by Rose that heavily infected snails do not propagate as infection with cercariæ destroys the genital processes.

CHAPTER XLII

PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES: FILARIASIS

Definition.—Morbid conditions produced by certain nematode worms, or filariæ, the adults of which, of both sexes, live in the lymphatics, connective tissues, or mesentery, producing live embryos or microfilariæ, which find their way into the blood-stream, where they are capable of living for a considerable time without developing further.

History.—In 1863 Demarquay found what is now known as the embryonic form—microfilaria bancrofti (Fig. 128, *1*) in hydrocele fluid, and in 1866 Wucherer discovered the same organism in chylous urine. In 1872 Lewis established the fact that the organism lives principally in the blood of man, and consequently named it *Filaria sanguinis hominis*. The adult was found in 1876 by Bancroft in Brisbane, and named *Filaria bancrofti* by Cobbold.

Manson in 1878 made the important observation that the mosquito subserved the parasite as intermediary host, and in 1880 described the remarkable phenomenon of filarial periodicity.

Originally Manson proposed to call the embryonic form of *Wuchereria bancrofti*, in order to emphasize its nocturnal periodicity, *Filaria nocturna*, but, in accordance with the rules governing zoological nomenclature, precedence must be given to Cobbold's name for the adult form; the embryonic form is therefore referred to in this manual as microfilaria bancrofti; the other filariæ of the blood are named microfilaria loa (or mf. diurna) (Fig. 128, *2*), microfilaria malayi (Fig. 128, *3*), microfilaria volvulus (Fig. 128, *4*) microfilaria ozzardi (mf. demarquayi) (Fig. 128, *6*) and microfilaria perstans, the embryo of *Acanthocheilonema perstans* (Fig. 128 *5*). Recently, *Filaria bancrofti* has, on zoological grounds, been renamed by systematists *Wuchereria bancrofti*.

Pathological importance.—Only one of these parasites, so far as we know at present—appears to have important pathological bearings, viz. *W. bancrofti*, which, in its adult stage, inhabits the lymphatics of man. There is abundant reason to believe that *W. bancrofti* is the cause of endemic chyluria, of various forms of lymphatic varix, and of other obscure tropical diseases, including tropical elephantiasis.

The filariæ less important from a pathological standpoint are dealt with in the Appendix (pp. 960–963).

I. FILARIASIS DUE TO WUCHERERIA BANCROFTI (FILARIA BANCROFTI)

Geographical distribution and prevalence.—*Wuchereria bancrofti* occurs indigenously in almost every tropical and subtropical

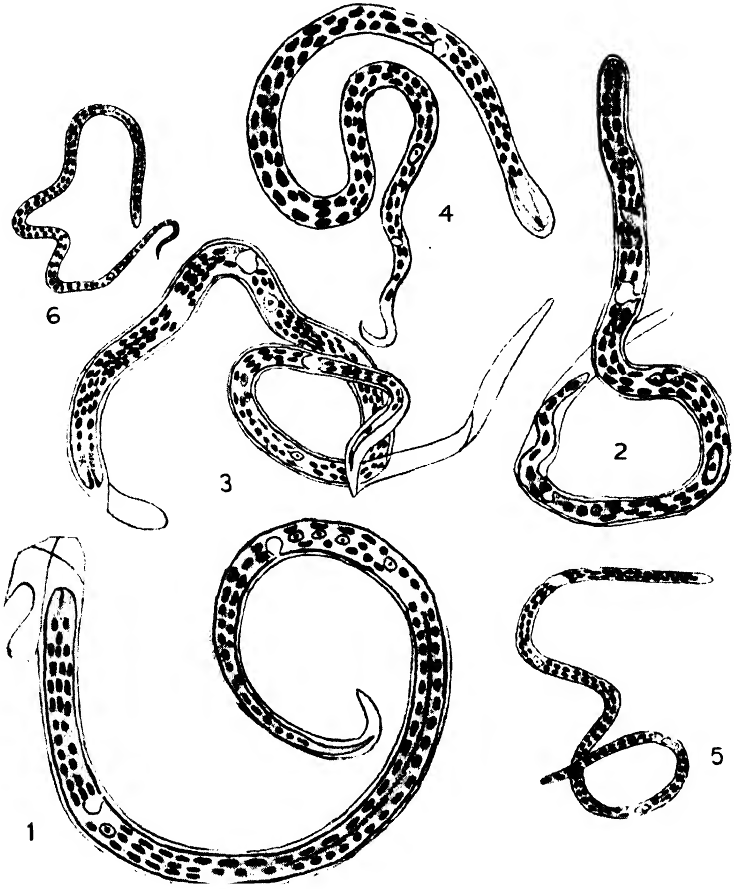


Fig. 128.—Human microfilariæ ; 1, Mf. bancrofti ; 2, Mf. loa; 3, Mf. malayi 4, Mf. volvulus ; 5, Mf. perstans ; 6, Mf. ozzardi. (*Drawn to scale.*)

country, from Charleston in the United States and Southern Spain in Europe to Brisbane in Australia. It is extremely common in India and South China, Samoa, and many of the Pacific islands, where fully 60 per cent. of the inhabitants are affected.

If the individuals who exhibit the microfilaria in their blood be reckoned in addition to those who exhibit the pathological effects of filarial disease, but in whose blood the microfilaria is no longer to be found, the incidence of filarial disease in some of the Pacific islands is a very high one—as high as 80 per cent. The parasite is common in South America, the West Indies, West and Central Africa. (MapVI.)

Ætiology. *Parental forms.*—The parent filariæ (*Wuchereria bancrofti*) have been found many times. They are long, hair-like, transparent nematodes, 2–3 in. in length (Figs. 129, 130). The sexes

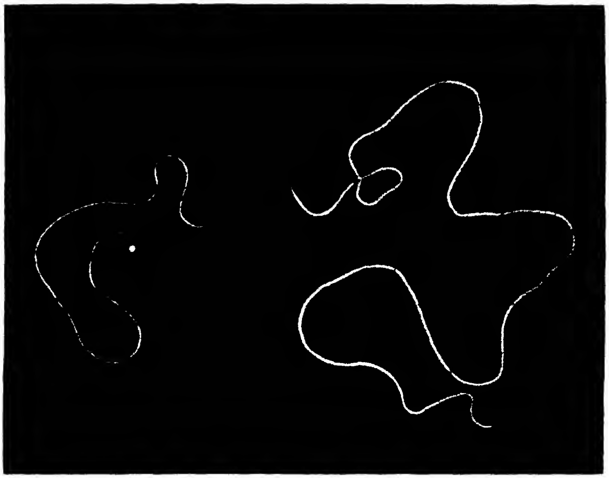


Fig. 129.—**Wuchereria bancrofti** (*enlarged*), *left, male ; right, female.* (*Dr. M. Oesterlein.*)

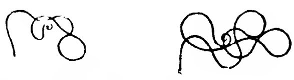


Fig. 130.—**Wuchereria bancrofti** (*natural size*), *left, male ; right, female.*

live together, often inextricably coiled about each other. Sometimes they are enclosed, coiled up several in a bunch and tightly packed, in little cyst-like dilatations of the distal lymphatics (Maitland) ; sometimes they lie more loosely in lymphatic varices ; sometimes they inhabit the larger lymphatic trunks between the glands, the lymphatic glands themselves, and, probably not infrequently, the thoracic duct.

The female worm is almost twice the length of the male, and considerably broader. The fully-mature and fecundated female filaria gives birth during her lifetime to an unending stream of living embryos, or microfilariæ, which emerge from the vaginal orifice. (For further details see Appendix p. 949.)

The life-spans of *W. bancrofti* and its microfilariæ have not been determined. From the fact that the microfilariæ have been found in the blood

long after the opportunity of infection has passed, it is to be concluded that the adults may live for many years. The embryo filariæ sometimes disappear completely from the circulation within a few hours of the death of the parent worms during an attack of lymphangitis.

As shown by Wise and the Editor, the mature worm is cretified after its death, and may be found in this condition in the lymphatic vessels and glands, sometimes in large numbers (Fig. 131), and it has been found by the Editor originally later by O'Connor and Elsbach, that the adult filariæ, whether alive or dead, cause occlusion of the lymph vessels and thereby contribute towards the general lymph stasis.

According to O'Connor the microfilariæ are destroyed in the substance of the lymphatic glands and are responsible to some extent for the pathological changes found in these structures. He has shown that they are broken up in the lymph-node sinuses, and that this is the common method of destruction of foreign substances in lymph-glands has been demonstrated by Indian-ink injection methods by Drinker, Wislicki and Field.[1]

The microfilariæ.—When present in large numbers in the blood-stream, microfilariæ may be recognized in wet film preparations; but, when the parasites are scanty, for the examination of a large number of persons it is often necessary to examine a considerable quantity of blood (20 c.mm.) in thick-drop preparations, dried and then dehæmoglobinized. When seen in fresh blood the embryo filaria is a snake-like organism which, without materially changing its position, wriggles about very actively.

When dead and stained, the embryo is seen to be enclosed in a sheath (Fig. 132). On measurement, it is found to be a little under 0·3 mm. in length, in breadth about the diameter of a red blood-corpuscle. At the anterior extremity of the living microfilaria can be seen a minute spicule, which is shot out and as rapidly retracted, and it is thought by some that the head is sheathed by a serrated "prepuce." In a fresh blood preparation the spicule can be seen disturbing cells at some distance away. (Fig. 133.) The utility of this mechanism is not known. Manson, who observed a similar mechanism in other microfilariæ, including those of birds, suggested that they subserved a necessary function in periodicity—the microfilariæ being enabled to affix themselves to the walls of the capillaries by these means, thus enabling them to maintain their station in the blood-stream during the hours of daylight.

Brug and Rodenwaldt have described in the Dutch East Indies a new microfilaria (*Filaria malayi*) which has a wide range in Malaya, Ceylon, India, Dutch East Indies, Indo-China, and South China (Fig. 128, *3*). Development takes place in a number of mosquitoes of the genera *Mansonioides* and *Anopheles*.

Filarial periodicity.—A singular feature in the life of the microfilaria is what is known as "filarial periodicity."

If, under normal conditions of health and habit, the blood be

[1] McMullen (1937) has described a case in an Indian, infected with *W. bancrofti*, in whom the microfilariæ were detected by means of the slit lamp, in the anterior chamber of the eye. No visible eye lesions were present. (*See* p. 787.)

Fig. 131. Calcified *Wuchereria bancrofti* lying in and blocking a lymphatic vessel. (*Orig.*)

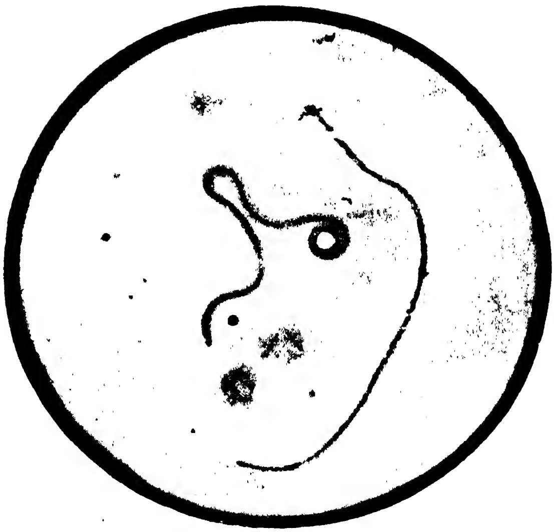


Fig. 132.—Microfilaria bancrofti in hydrocele fluid. The embryo on the right has escaped from its sheath. (*Orig.*)

examined during the day, the microfilaria is rarely seen, or, if it be seen, only one or two specimens at most are encountered in a slide. But towards evening they begin to appear in gradually increasing numbers. The swarm goes on increasing until about midnight, at which time it is no unusual thing to find as many as three hundred, or even six hundred in every drop of blood; so that it has been

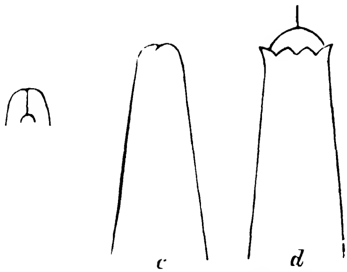


Fig. 133.—Structure of head end of microfilaria perstans (*a*, *b*) and of microfilaria bancrofti (*c*, *d*).

calculated that as many as forty or fifty millions are simultaneously circulating in the blood-vessels. After midnight the numbers begin gradually to decrease; by eight or nine o'clock in the morning the microfilariæ have disappeared from the peripheral blood for the day. This nocturnal periodicity, under normal conditions, is maintained with the utmost regularity for years. Should, however, as Mackenzie

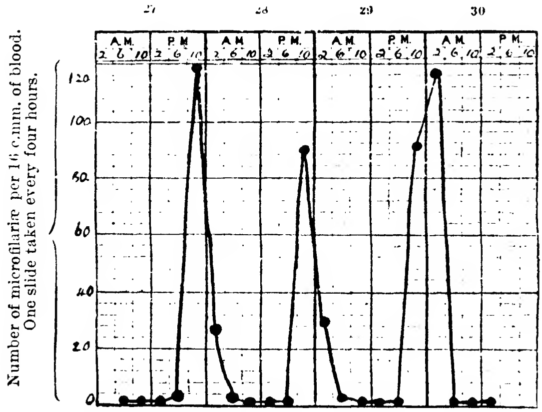


Chart 27.—Filariasis (*W. bancrofti*, microfilaria nocturna), showing nocturnal periodicity. (*Orig.*)

has shown, a filarial subject be made to sleep during the day and remain awake at night, after a period of three to four days the periodicity is reversed; that is to say, the parasites come into the blood during the day and disappear from it during the night. It cannot

be the sleeping state, as some have conjectured, that brings about this periodicity ; for the ingress of the microfilariæ into the peripheral blood commences three or four hours before the usual time for sleep. and the egress several hours before sleep is concluded, and this egress is not complete until several hours after the usual time of waking. This night swarming of the embryos of *W. bancrofti* in the peripheral circulation is apparently an adaptation correlated to the life-habits of its liberating agent, the mosquito *Culex fatigans*, its usual intermediary host. (Chart 27.)

Many years ago Manson had an opportunity of ascertaining that

Fig. 134. Section of lung showing microfilariæ in blood-vessels.
(*Photomicro : Dr. Spitta.*)

during their diurnal temporary absence from the peripheral circulation the microfilariæ retire principally to the larger arteries and to the lungs, where, during the day, they may be found in enormous numbers.

In lung sections (Fig. 134) the microfilariæ lie outstretched or variously coiled in the vessels, large and small. In the heart-muscle they are found in the capillaries between the fibres; in the kidneys they seem especially to affect the Malpighian tufts ; a very few are also found in the capillaries of the brain ; vast numbers are present in smears from the inner surface of the carotid arteries. Preparations afford no explanation as to how the microfilariæ contrive to maintain their position in the blood-current, or as to the forces determining their peculiar distribution.

Subsequent observations have shown that, though microfilariæ can be demonstrated in the capillaries of the liver and spleen in small numbers, the capillaries of the lung and kidney (Anderson) appear to be the favourite habitat of the embryos of *W. bancrofti*, and of other species which do not exhibit this extraordinary nocturnal periodicity. Thus, the non-periodic

Pacific microfilaria (see below) has also been found in greatest abundance in these situations.

Low, together with the Editor and Walters, has shown that, though the periodicity curve is absolutely nocturnal, yet embryos may be present in small numbers in the peripheral blood in the daytime. The evening rise of the embryo filariæ is much more gradual than the matutinal fall, and the maximum migration of embryos occurs at 2 a.m. A fall occurs, however, immediately the waking state is entered upon. The number of microfilariæ in an infected patient remains remarkably constant: Low and the Editor observed the periodicity curve in one case for a period of twelve years.

Various theories have been advanced by Fülleborn and others to account for this singular phenomenon, though none are entirely satisfactory. Yorke and Blacklock think that obstruction to the passage of microfilariæ through the cutaneous vessels is at a minimum at the end of the period of bodily activity, and that the periodicity is primarily dependent upon the variations in the actual supply of microfilariæ to the cutaneous vessels. But how account for the diurnal periodicity of microfilaria loa in circumstances which are exactly the reverse, or for the non-periodicity of the Pacific form of *W. bancrofti?*

Clayton Lane believes that periodicity can best be explained by a process of periodic cyclical parturition on the part of the female filaria, with a daily destruction of all the embryos, and this hypothesis has received some support from the observation of O'Connor. He has found that the uterus of the female adult filaria removed at operation empties its contents of microfilariæ so that they should be present in the blood during the hours of night. The life-span of the individual microfilaria in the blood-stream has not been accurately ascertained but it is certainly longer than 24 hours: on a slide at 4° C. they have been kept alive for six weeks by the Editor in 1910, and later by Rao. Kubo has actually shown that in *Dirofilaria immitis* there is also a seasonal variation, and that in China the maximal numbers of microfilariæ are found in the circulation during the hot weather at the end of August and beginning of September: the minimal numbers in November and December.

Joyeux and Sautet have found that this microfilaria actually grows in length on favourable artificial media outside the body.

In the case of the dog heart-worm, *Dirofilaria immitis*, strong evidence has been now adduced by Hinman, Faust and de Bakey (1934) that the periodicity phenomenon cannot be explained on the basis of cylical parturition. By transfusing heavy parasitized blood into an unaffected dog, using 140 c.c. of blood, containing 27,475 microfilariæ, after previous removal of an equal amount of blood, it was estimated that 9,000 microfilariæ per c.c. would appear in the circulation of the recipient, but actually only 5 per cent. did so. The microfilaria count of the donor was remarkably reduced for six days, but returned to its original level in two weeks. Active microfilariæ were found in the recipient's blood for ten weeks. Definite nocturnal periodic variations has been observed in the microfilariæ of *Dirofilaria immitis*, and also in the analogous species in the American crow (p. 950).

Non-periodic microfilaria bancrofti.—Formerly it was thought that nocturnal periodicity was uniformly observed by the microfilaria of *W. bancrofti* at all times and in every country. Many years ago Thorpe remarked that in Tongo and Fiji the microfilaria could be found often in great abundance in the blood during the daytime, but, strange to say, it has been ascertained

that the microfilariæ of neighbouring islands in the Pacific—namely, the Solomons, some parts of New Guinea and of the Bismarck Archipelago—are for the most part, though not entirely, periodic.

The Editor demonstrated that the microfilariæ of Indian immigrants who have acquired their filarial infections in India retain their periodic habits during at least three years of residence in Fiji, but that if an Indian or a Solomon Islander acquires the infection in Fiji the microfilariæ are non-periodic in habit.

As an explanation of this striking anomaly, it has been suggested that the non-periodic microfilaria is the progeny of a parent worm specifically distinct from *W. bancrofti*; but Leiper failed to find any anatomical difference between the Fijian worm and the *W. bancrofti* of India, China, and South America, but it may yet be proved that the non-periodic variety is a separate biological species which produces certain distinct pathological peculiarities. Fülleborn and the Editor, after minute study and comparison of the histology of the microfilariæ from those countries, find that they are identical in every respect. It may be, as the Editor suggested, that the non-periodic habit of the Pacific microfilaria is a partial adaptation to the day-habit of the usual intermediary of the parasite in Fiji and other Pacific islands—*Aëdes variegatus* (*Stegomyia pseudoscutellaris*) (Plate VIII; 1). These observations have been abundantly confirmed by O'Connor, who has established the significant fact that the range of the non-periodic filaria is coextensive with that of its intermediary host, *Aëdes variegatus*, in the Pacific.

Fig. 135. Microfilariæ casting their sheaths.

The mosquito the intermediary host of W. bancrofti.—Should the females of certain species of mosquito[1] (*Culex fatigans*[2] *Aëdes variegatus*) which have fed on the blood of a filaria-infected person be examined immediately after feeding, the blood contained in the stomach will be found to harbour large numbers of living microfilariæ, while a few hours afterwards it will be seen that many of them are actively engaged in endeavouring to escape from their sheaths. The change in the viscosity of the blood seems to prompt them to endeavour to effect their escape. After a time the majority succeed in effecting a breach and in wriggling themselves free from the sheaths which had hitherto enclosed them (Fig. 135). This process can be induced by chilling wet blood preparations on ice and then allowing them to thaw at room-temperature. The microfilariæ now, having become free, move about from place to place. At a somewhat later period it will be observed that after discarding their sheaths, they have quitted the stomach and entered the thoracic muscles of the

[1] For a complete list of species which may serve as intermediary hosts, see Appendix, p. 953.
[2] In China, *Culex pipiens* (see p. 953).

mosquito, where they may be seen moving languidly. To detect this, one should dissect the insects in normal saline solution, for if distilled water is used, the larval worms break up by osmosis. In the thorax of the insect the parasite enters on a metamorphosis which takes from ten to twenty days (according to atmospheric temperature) to complete, eventuating in the formation of a mouth, of an alimentary canal, and of a peculiar trilobed caudal end, as well as in a relatively enormous increase in size (to $\frac{1}{16}$ in.) and activity. During this period the larva sheds its cuticle (ecdysis) twice. The larval filariæ now leave the thorax, and the majority pass forwards by the prothorax and neck, and, entering the head, coil themselves up close to

Fig. 136.—*W. bancrofti* **in head and proboscis of mosquito.** (*G. C. Low.*)
a, a, a, Filariæ; *b*, labium; *c*, labrum: *d*, base of hypopharynx; *e*, duct of veneno-salivary gland; *f, f*, cephalic ganglia; *g, g*, eye; *h*, œsophagus; *i*, pharyngeal muscle.

the base of the proboscis beneath the pharynx and cephalic ganglia, though a few find their way into the abdomen, and even into the legs. Low first showed that the filaria, in its future progress, enters the proboscis, where, as pointed out by Grassi, its exact position is the interior of the proboscis-sheath (labium) (Fig. 136).

The parasites remain in the proboscis, awaiting an opportunity to enter a warm-blooded vertebrate host, when the mosquito next proceeds to feed. This they appear to do by penetrating the thin membrane that unites the labella to the tip of the proboscis-sheath, and so pass on to the surface of the skin, which they penetrate in the neighbourhood of the puncture made by the mosquito. As pointed out by Annett and Dutton, there is a weak point in the chitinous skeleton of the labium just where the labella are joined on, and it is at this spot that the parasites escape. Sometimes the larval

filaria, in its progress through the thorax, becomes arrested and dies; the defunct worm then appears to become enclosed, like a mummy, in a case of chitin inside the mosquito's body, resulting in the curious structure represented in Fig. 137. For further zoological studies, *see* Appendix p. 951.

Mechanism of blood suction in mosquitoes.—Fülleborn concluded that blood-sucking in mosquitoes is a reflex action. The fluid is aspirated by the initiatory gulp-like working of the insect's sucking pump, and when the mouth cavity is full of fluid, the spasmodic action of the pump becomes converted into a more or less continuous flow until the abdomen is fully distended. This has been confirmed by Macgregor.

Fig. 137.—Chitinized filaria in thorax of mosquito.

These observations prove that, like the malaria parasite, the filaria is introduced into its human host through the agency of a mosquito-bite. Once introduced into the human body, the filaria finds its way into the lymphatics and glands. Arrived in one of these, it attains sexual maturity; possibly, though no exact data are available, after a period of six months or more fecundation is effected, and in due course new generations of embryo filariæ (microfilariæ) are poured into the lymph. These, passing through the gland—if such should intervene—by way of the thoracic duct and left subclavian vein, or by the lymphatics of the upper part of the body, finally enter the circulation.

Epidemiology and endemiology.—In most countries in which filariasis is common it appears to be the rule that the incidence of infection is greatest in the male sex, though, in British Guiana, Daniels and Conyers reported twice as many females infected as males. This exception to the general rule probably finds an explanation in the habits of the natives. The Editor's statistics from Fiji show that of 1,320 people of Fijian blood, 30·4 per cent. of males and 23·9 per cent. of females were filariated. The incidence is greatest in both sexes after the twentieth year; comparatively more females than males are infected below the age of ten. The youngest infected subject is one recorded by Anderson and his colleagues in British Guiana—a child of 14 months. The rate of filariation varies considerably in different islands of the Pacific, and even in different districts of the same island, and is in direct proportion to the incidence of elephantiasis and other filarial diseases. In an investigation conducted in 1912 in Ceylon the Editor found that, whereas 26 per cent. of the adults of some of the villages were infected, in neighbouring ones the inhabitants were quite free from the parasite and its associated diseases.

Pathology. *The filaria not generally pathogenic.*—In most cases of filarial infection the parasite exercises no manifest injurious influence whatever. In a certain proportion of instances, however, there can be no doubt that it does have a very prejudicial effect, and this mainly by obstructing lymphatics. The healthy, fully-formed microfilariæ—

that is to say, the embryonic filariæ which, by means of the microscope, we see in the blood—are, so far as we can tell, particularly harmless.

Filarial disease originating in injury of lymphatic systems.—Roughly speaking, the filaria causes two types of disease: one characterized by varicosity of lymphatics, the other by more or less solid œdema. The exact way in which the parasite operates has not been definitely and absolutely ascertained for all types of filarial disease. Apparently, in some instances a single worm, or a bunch of worms, may plug the thoracic duct, and act as an embolus or originate a thrombus; or, the worm may give rise to inflammatory thickening of the walls of

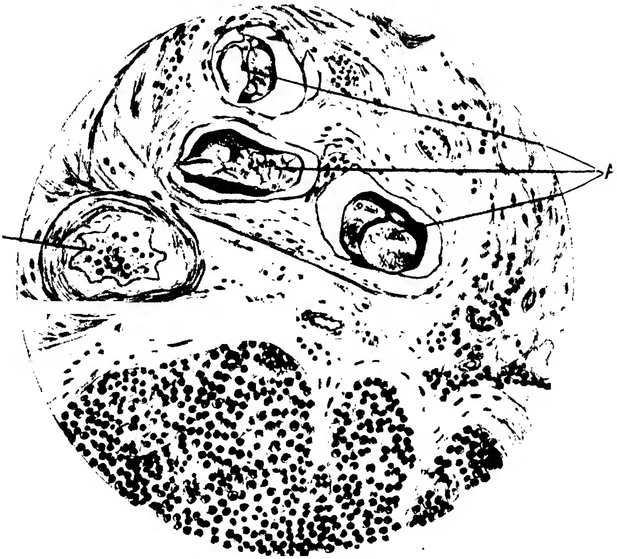


Fig. 138.—Section of a fibrosed lymphatic gland. (*Orig.*)
A, Portions of a calcified *W. bancrofti*; B, partially occluded lymphatic vessel.

this vessel, and so lead to obstruction from the consequent stenosis or thrombosis. In other instances the minor lymphatic trunks and the glands may be similarly occluded. (Figs. 138, 139.)

The Editor's work in Fiji has shown that the afferent lymphatic glands situated at some considerable distance from the actual seat of the filaria worms, for instance, the lumbar glands, undergo considerable changes, such as fibrosis, focal necrosis, and giant-cell formation. These changes may be due partly to the destruction of microfilariæ within the gland substance, or to toxins actually excreted by the adult worms. It is known from the work of O'Connor that some of the microfilariæ undergo calcification in this situation, and that, moreover, they cause endothelial proliferative outgrowths in the lumen of the lymphatic channels.

Serological and intradermal tests in filariasis.—These tests have been introduced by Fairley and independently by Taliaferro and Hoffman. The antigen is made from *Dirofilaria immitis* of the dog, which is washed and dried, it being estimated that 1 grm. of this substance contains 250–300 worms. Alcoholic is more potent than is saline extract of the antigen. A positive complement-deviation test is given with most cases of

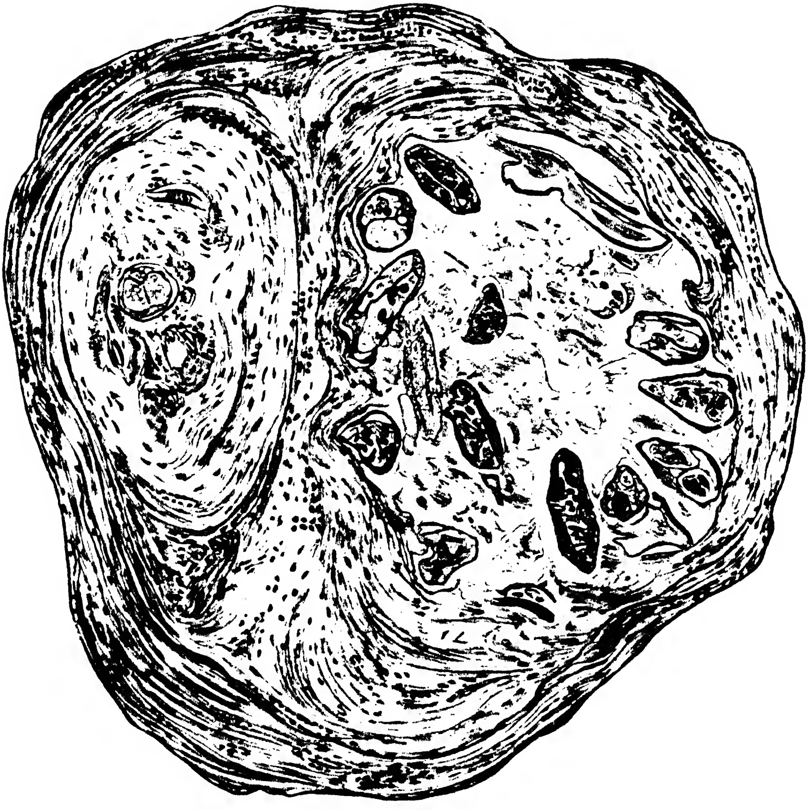


Fig. 139.—Section of a thickened brachial lymphatic containing portions of dead filariæ undergoing disintegration and blocking the lumen of the vessel. Note the large amount of fibrosis. (*Orig.*)

W. bancrofti filariasis; but the reaction is a group one and appears to be more reliable in *L. loa* infections than in *W. bancrofti* and is also positive in *Onchocerca volvulus*. Lloyd and Chandra have obtained the most reliable results with an antigen derived from the acetone-insoluble lipoids of *D. immitis* in the process used by Bordet and Ruelens for syphilitic antigen.

The intradermal test is based on the same immunological principles as are other tests of this nature. Fairley uses 0·25 c.c. of a 0·1-per cent. extract as antigen. An immediate (30 min.) and delayed reaction are obtained; the

latter may become indirect after a period of forty-eight hours. A wheal over 2 cm. in diameter is regarded as positive.

Technique. *Preparation of antigen for complement-deviation test.*—A technique similar to that described for bilharzia cercarial antigen is employed, 0·5 grm. of the dried powdered *Dirofilaria immitis* being extracted with 50 c.c. of 98-per-cent. alcohol for 24 hours at 37° C. Well shaken by hand several times during this period, it is filtered through Whatman No. 1 and a Buchner filter. The filtrate is subsequently concentrated by bubbling air through the solution kept at a temperature of 40° C. by immersion in a water-bath till turbid; this turbidity is then removed by adding 8 c.c. of fresh alcohol, making the total volume 25 c.c. The resulting extract is then stored in the ice-chest in dark ampoules of 1 c.c. capacity. The technique of putting up the test is similar to the standard advocated for the serological diagnosis of bilharziasis.

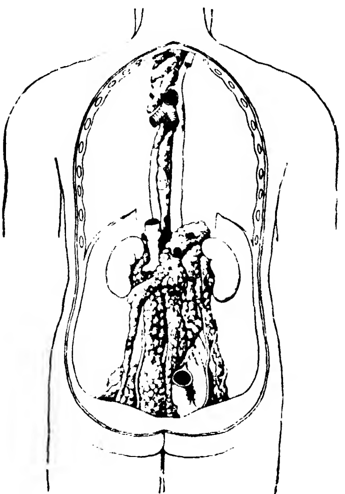


Fig. 140.—Dissection of the lymphatics in a case of chyluria, showing the dilated right and left renal lymphatics and the thoracic duct. (*Mackenzie*, "*Trans. Path. Soc. Lond.*")

Preparation of antigen for intradermal test.—Fifty c.c. of a 1-per-cent. saline extract of dried powdered antigen is incubated for two hours at 37° C., being well shaken by hand from time to time. Subsequently it is passed through a Whatman No. 1 filter paper and then a Buchner filter, and is then sterilized by passage through a sterile Seitz asbestos filter. The filtrate is put up in dark glass ampoules and stored on ice.

Pathology of lymphatic varix.—In consequence of the rich anastomosis existing between the contiguous lymphatic areas, on filarial obstruction occurring in one of them a compensatory lymphatic circulation is sooner or later established. But before this can be thoroughly effected a rise of lymph-pressure and a dilatation of the lymphatics in the implicated area must take place. This leads to lymphatic varix of different kinds, degrees, and situations. When the seat of filarial obstruction is the thoracic duct, the chyle poured into that vessel can reach the circulation only by a retrograde movement; this fluid may therefore be forced to traverse in a retrograde way the abdominal and pelvic lymphatics, the lymphatics of the groin, scrotum, and abdominal wall. As a consequence, these vessels, together with the thoracic duct up to the seat of obstruction, become enormously dilated. In dissections of such cases (Fig. 140) the thoracic duct has been found distended to the size of a finger, the abdominal and pelvic lymphatics forming an enormous varix, perhaps a foot in diameter and some inches in thickness, concealing kidneys, bladder, and spermatic cords. In such cases when one of the vessels of the varix is pricked or ruptures, the contents are found to be white or pinkish. They are not limpid like ordinary lymph. They are chyle, therefore—chyle on its way to enter the circulation

by a retrograde compensatory track. When the varix involves the integuments of the scrotum, the result is "lymph scrotum"; when most prominent in the groin, then a condition of glands is produced which Manson called "varicose groin-glands"; when the lymphatics of the bladder or kidneys are affected and rupture from over-distension, then chyluria is the result; when those of the tunica vaginalis rupture, then there is chylous dropsy of that sac —"chylocele"; the same may happen in the peritoneum —chylous ascites. Occasionally varicose lymphatic glands, resembling those frequently encountered in the groins, are found in the axilla. Occasionally, also, limited portions of the lymphatic trunks of the limbs are similarly and temporarily, or more permanently, distended. This, doubtless, is the pathology of all those forms of filarial disease characterized by visible varicosity of lymphatics, with or without lymphorrhagia. It may happen that the obstruction is in some lymphatic tract on the distal side of the entrance of the chyle-bearing vessels into the receptaculum chyli. In this case a rupture of the consequent lymphatic varix will give issue to a limpid lymph unmixed with chyle.

In filarial disease associated with lymphatic varix, microfilariæ are generally present in the blood, as well as in the contents of the dilated vessels. Sometimes, it is true, the microfilariæ are not found. Such cases are probably of long standing; had the microfilariæ been looked for at an earlier stage of the disease, they would presumably have been discovered.

The microfilariæ have been seen to vanish from the blood-stream by various observers; doubtless this is due to the death of the parent parasite, and is generally associated with an attack of lymphangitis.

Pathology of elephantiasis. *Reasons for regarding elephantiasis as a filarial disease.*—(1) The geographical distribution of *W. bancrofti* and that of elephantiasis correspond; where elephantiasis abounds there the filaria abounds, and *vice versa*. (2) Filarial lymphatic varix and elephantiasis occur in the same districts, and frequently concur in the same individual. (3) Lymph scrotum, unquestionably a filarial disease, often terminates in elephantiasis of the scrotum. (4) Elephantiasis of the leg sometimes supervenes on the surgical removal of a lymph scrotum. (5) Elephantiasis and lymphatic varix are essentially diseases of the lymphatics. (6) Filarial lymphatic varix and true elephantiasis are both accompanied by the same type of recurring lymphangitis. (7) As filarial lymphatic varix is practically proved to be caused by the filaria, the inference appears to be warranted that, with rare exceptions, the elephantiasis of warm climates—the disease with which lymphatic varix is so often associated and has so many affinities—is attributable to the same cause.

If the filaria be the cause of tropical elephantiasis, how account for the absence of the embryos from the blood, as is the case in the majority of instances of this disease? The answer is: Either the disease-producing filariæ have died; or the lymphatics draining the affected area are so effectually obstructed by the filaria, its products, or its effects, that any microfilariæ they may contain, or may have contained, cannot pass along these vessels to enter the circulation. Adult filariæ of both sexes in large numbers may be found in enlarged fibrosed lymphatic glands—epitrochlear, for example—without the presence of the corresponding microfilariæ in the blood-stream.

We have already seen that in filarial lymphatic varix the parasites which produced the disease may die, particularly during attacks of lymphangitis;

we have also seen that they may become cretified and may be found in large numbers in this condition or alive in the glands and lymphatic trunks, where, as the Editor has shown, they give rise to giant-cell formation and fibrotic changes of an obstructive nature (Fig. 139).

Furthermore, in filariated subjects a process of proliferation of the endothelium of the lymphatic vessels takes place—a species of lymphangitis, first described by the Editor and later confirmed by O'Connor; it is due to the action of the microfilariæ which become imprisoned in the endothelial lining of the vessel (Fig. 141).

There is quite enough to show that pathological of

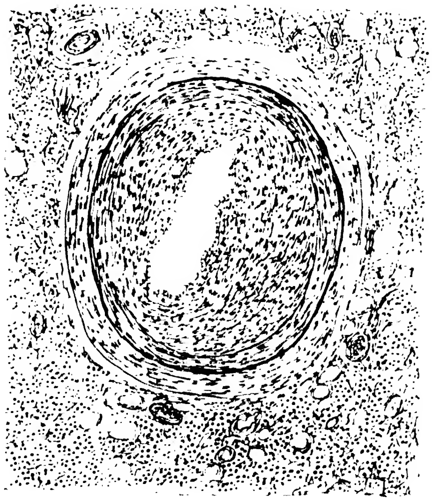


Fig. 141. Occlusion of lymphatic vessels by proliferation of the endothelium in filariasias. (*Orig.*)

elephantiasis lies in the destruction and blockage of the lymphatic filters in the lymphatic glands.

For the true understanding of elephantiasis it is necessary to give a few facts about the known physiology of the lymphatic system. Lymph is a transudation from the veins and its production is maintained and regularized by intravenous pressure. It appears that, in order to produce true elephantoid tissue, a transudation of lymph must take place, and that this transuded lymph must contain an excess of protein; this forms an ideal culture medium for proliferating cells, thereby producing lymphous hyperplasia.

Superficial lymphatic capillaries are specially abundant and contain actively circulating lymph. The lymph stream flows in a series of directions from different areas of skin, with sharp lines of demarcation between each; therefore the former conception of a generalized lymphatic anastomosis is incorrect. Forming, as they do, the most important and extensive part of

the lymphatic system, the superficial lymphatics show the most pronounced changes in the integument and subcutaneous tissues. Woollard and Gray have demonstrated that the lymphatic supply of the skin is particularly rich, and that the vessels lie mainly in the superficial part of the dermis at a slightly deeper plane than the arterioles, which give off loops to the dermal papillæ. There is also a wide-mesh plexus of fairly straight vessels lying parallel to the skin surface, and these particular vessels contain no valves. In the deeper layers the lymphatics from a series of collecting radicles rather than a true plexus; they are joined to the superficial plexus by more or less vertically placed vessels, and the collecting trunks contain valves situated about 1 mm. apart. The deep fascia is devoid of lymphatics. There is, therefore, a clear separation of the superficial or external lymphatic system from the deep or internal system.

The anatomical situation of elephantiasis depends, therefore, upon the anatomical distribution of the afferent lymphatic vessels. It must not be thought, however, that lymphatic elephantiasis is *solely* the product of filarial infection. The following classification of elephantiasis is suggested by the Editor:

(*a*) Congenital or familial elephantiasis (Milroy's or Meige's disease); stenosis of main lymphatic trunks.
(*b*) Parasitic elephantiasis: *Wuchereria bancrofti*, or *Onchocerca volvulus*.
(*c*) Septic elephantiasis (*Elephantiasis nostras*—lymphatic infection by streptococci).
(*d*) Toxic elephantiasis by absorption of irritating toxins, such as chrysarobin.
(*e*) Obstructive elephantiasis, due to tuberculous glands, carcinomatous growths, syphilis, or yaws, or to surgical removal of main chains of glands.
(*f*) Venous elephantiasis secondary to venous thrombosis, such as *phlegmasia alba dolens*, or white leg, in parturient women.

Tesch, Brug and others have shown that elephantiasis is also produced by *Filaria malayi*. The difference between the two forms of lymphatic obstruction seems to lie in the predilection of this form for the legs rather than for the genitalia and the scrotum as in *Wuchereria bancrofti* infections.

In most cases the real origin of the obstruction lies in the fibrotic changes induced by the parasite in the lymphatic vessels and glands, leading to elephantiasis. Lymph stasis in the lymphatic vessels alone does not produce elephantiasis; this has been proved by ligature of the lymphatic trunk, which results in œdema but not in true elephantoid hypertrophy.

Anderson believed that the adult filariæ living in the lymphatic system, by the damage they produce in the intima of the vessels, so prepare the way that a streptococcal or staphylococcal infection, however mild, is able to obtain a foothold and that by

the changes thus produced the lymph-channels become further occluded.

O'Connor has now shown that in cases of filarial lymphangitis focal spots can be distinguished from which the inflammatory process appears to commence, and that this phenomenon indicates the site of a dead filaria worm; furthermore that an attack of lymphangitis may be cut short by the injection of sulpharsphenamine (0·2 grm. dissolved in 2 c.c. sterile 1-per-cent. novocain). This observer, together with Golden and Auchincloss, has also shown that in filariated subjects, especially in elephantiasis, calcified filariæ may be demonstrated by means of X-rays. The shadows range from 1 mm. in width to 2–3 mm. in length. These studies seem to indicate that the infection may be quite extensive. Fifteen shadows, or groups of shadows, were detected in one elephantoid leg.

In these ways one can explain the production of elephantiasis by the filaria, and the absence from the blood of the embryos of the parasite which started the disease. The latter cannot pass the occluded glands. Very likely the parent worm, or worms, die at an early stage of the disease, killed by the subsequent lymphangitis, or some other indetermined cause.

The subjects of elephantiasis less liable than others to have microfilariæ in their blood.—Why should elephantiasis cases have proportionately fewer microfilariæ than the non-elephantiasis cases? The answer may be that in the former the existence of elephantiasis implied that a large area of their lymphatic systems was blocked, and the blood could be stocked with microfilariæ carried by the lymph from only a relatively small lymphatic area; and that there was therefore a proportionately lesser likelihood of the parent filariæ having for their young an unobstructed passage to the blood.

This apparent anomaly is found in other conditions produced by *W. bancrofti.* In Fiji, for instance, the Editor observed that 38·2 per cent. of the cases of elephantiasis he saw harboured microfilariæ, while the microfilariæ-rate in cases of glandular enlargement, also of filarial origin, was 34·6 per cent. On examining all those with clinical manifestations of filarial disease, it was found that 19·7 per cent. thus affected had microfilariæ in the blood, but that no less than 44·8 per cent. of those with numerous microfilariæ showed no obvious sign of disease whatever. As in the case of *Filaria malayi*, it is possible that the non-periodic *W. bancrofti* in the Pacific produces its own pathological picture. This latter filaria lives mostly in the lymphatic glands and produces phenomena which are connected with these structures. It has a special preference for the epitrochlear glands, and is therefore liable to produce elephantiasis of the arms. It does not produce either chyluria or lymphuria as does the periodic form of *W. bancrofti.*

Symptoms, Diagnosis, and Treatment of Filarial Diseases

Enumeration of filarial diseases.—The diseases known to be produced by or associated with *W. bancrofti* are—abscess; lymphangitis; arthritis; synovitis; abscess of hip-joint; varicose groin glands; varicose axillary glands; lymph scrotum; cutaneous and

deep lymphatic varix; orchitis; funiculitis; chyluria; elephantiasis of the leg, scrotum, vulva, arm, mamma, and other parts; chylous dropsy of the tunica vaginalis; chylous ascites; chylous diarrhœa, and probably other forms of disease depending on obstruction or varicosity of the lymphatics, or on the death or injury of the parent filariæ in a lymphatic abscess—including fatal peritonitis and secondary infections by pyogenic micro-organisms.

Abscess.—Occasionally, as already mentioned, whether in consequence of blows or other injuries, of lymphangitis, or of unknown causes, the parent filariæ die. Generally the dead body is absorbed, just as a piece of aseptic catgut would be, or becomes cretified.[1] Sometimes the dead worm acts as an irritant and causes abscess, in the contents of which fragments of the filaria may be found. Such abscesses, occurring in the limbs or scrotum will discharge in due course, or may be opened; if properly treated surgically, they may lead to no further trouble. Should they form in the thorax or abdomen, serious consequences and even death may ensue.

The starting-point of these abscesses is, possibly, a small hæmorrhage produced by the filaria worm itself which has become secondarily infected, but when no such occurrence takes place the defunct filaria becomes cretified. This condition must not be confused with a generalized pyæmic abscess, commonly found in the tropics and known as tropical pyomyositis. (*See* p. 705.)

Lymphangitis and elephantoid fever.—Lymphangitis is a common occurrence in all forms of filarial disease, particularly in elephantiasis, varicose glands, and lymph scrotum. When occurring in the limbs the characteristic painful cord-like swelling of the lymphatic trunks and associated glands, and the red congested streak in the superjacent skin, are usually apparent at the commencement of the attack. The attack may continue for several days, and be accompanied by severe headache, anorexia, often vomiting, and sometimes delirium. After a time the tension of the inflamed integuments may relieve itself by a lymphous discharge from the surface. Usually the attack ends in profuse general diaphoresis. Lymphangitis may be confined to groin glands, testis, spermatic cord (endemic funiculitis), or abdominal lymphatics. When it affects an extensive abdominal varix, symptoms of peritonitis are rapidly developed, and may prove fatal.

Observations by Anderson and others would indicate that a streptococcus is the initial cause of lymphangitis, but some at present regard it as a manifestation of an allergic reaction to the toxins of *W. bancrofti*. Morales-Otero and Pomales-Lebrón have shown that streptococci probably play some part in recurring lymphangitis, for soon after the first attack a high degree of antistreptococcal potency is

[1] Wise and Minett have found filariæ, living or cretified, in the following situations, viz.: pelvis of kidney (31 times), epididymis (18 times), retroperitoneum (12 times), the ilio-psoas muscle (4 times), Glisson's capsule (twice), inguinal glands (25 times), lymphatic vessels (8 times). Similar observations have been made by the Editor in Fiji.

developed in the blood. From this they conclude that attacks of lymphangitis are preceded by an infection with *Streptococcus hæmolyticus*.

In the Pacific islands a form of filarial fever is commonly met with in heavily-infected districts unassociated with signs of lymphangitis; in this form there is probably an inflammation of the deep-seated lumbar lymphatics or glands, which are not visible.

Diagnosis.—This fever, usually termed "elephantoid fever," occurs at varying intervals of weeks and months, or years, in nearly all forms of elephantoid disease. Its tendency to recur, the severe rigor, and the terminal diaphoresis, cause it to be mistaken for malaria. In Barbados, where there was until recently no malaria, it is habitually called "ague." In Samoa it is known as "mumu fever"; in Fiji as "wanganga." In the absence of the malaria parasite, there should be no difficulty in arriving at a diagnosis. At one time in India the recurrent fever was believed to depend upon mysterious lunar influences.

Treatment.—The treatment should consist in removing any cause of irritation, in rest, elevation of the affected part, cooling lotions or warm fomentations, mild aperients, opium or morphia to relieve pain, and, if tension is great, pricking or scarifying the swollen area under suitable aseptic conditions. Subsequently the parts, if their position permits, should be elevated and firmly bandaged. Following upon the work of the Editor, Wise, and Rose, suggesting that many of the symptoms of filariasis are of septic origin, Anderson obtained definite amelioration in his cases in British Guiana, and, in some instances, freedom from symptoms for a considerable period, by the injection of staphylococcal or streptococcal vaccines. Detoxicated vaccines gave slightly better results, though in each case the offending organism should, if possible, be determined. The initial dose should be ten million organisms; three or more injections should be given every third day till the maximum of fifty million is reached. Pons estimates that 40 per cent. of patients treated with streptococcal vaccines or with filtrates from cultures of these organisms (which appear to be more efficacious) are benefited to a marked degree.

Sulphanilamides are now being employed in treatment, and recently, good results have been recorded by the exhibition of proseptacine in 0·5 grm. doses given every four hours.

Varicose groin-glands (Fig. 142).—Varicose groin-glands are frequently associated with lymph scrotum, with chylous dropsy of the tunica vaginalis, or with chyluria. Occasionally all four conditions coexist in the same individual.

As a rule, the patient is not aware of the existence of these varicose glands until they have attained considerable dimensions. Then, a sense of tension, or an attack of lymphangitis, calls attention to the state of the groins, where certain soft swellings are discovered. These swellings may be of insignificant dimensions or they may attain the size of a fist. They may involve both groins, or only one groin; they

may affect the inguinal glands alone, or the femoral glands alone, or (and this is generally the case) both sets together.

Diagnosis.—It is important to be able to diagnose these tumours from hernia, for which they are often mistaken. This can be done by observing that they are not tympanitic on percussion; that though pressure causes them to diminish, they do so slowly; that there is no sudden dispersion accompanied by gurgling, as in hernia, on taxis being employed; that they convey a relatively slight or no impulse on coughing; that they slowly subside on the patient lying down, and slowly return, even if pressure be applied over the saphenous or

Fig. 142.—Varicose groin-glands and chylocele.

inguinal openings, on the erect posture being resumed. The cautious use of the hypodermic needle will confirm diagnosis, which may reveal tiny microfilariæ, or actually filarial eggs, and the diagnosis would be further strengthened by the coexistence of lymph scrotum, chyluria, or chylous hydrocele, and the presence of microfilariæ in the blood. *Chronic swellings about the groin, cord, testis, and scrotum in patients from the tropics should always be regarded as possibly filarial.*

Treatment.—Unless they give rise to an incapacitating amount of discomfort, and are the seat of frequent attacks of lymphangitis, varicose groin-glands are best left alone. Excision is not always satisfactory, as it may be followed by lymphorrhagia at the seat of

the wound, by excessive dilatation of some other part of the implicated lymphatic area, by chyluria, or by elephantiasis in one or both legs.

Similar varicose dilatation of the axillary glands is sometimes, though much more rarely, found. Bancroft designated these varicose axillary and groin glands " helminthoma elastica."

Cutaneous and deeper lymphatic varices.—Occasionally cutaneous lymphatic varices are seen on the surface of the abdomen, on the legs, arms, and probably elsewhere. Filarial lymphangiectasis of the spermatic cord is not uncommon. The contents may be milky and chylous, or straw-coloured and lymphous, according to situation and connections.

Thickened lymphatic trunks.—In cases of lymphangitis, after the initial swelling and inflammation have subsided, a line of thickening remains. On excising this thickened tissue and carefully dissecting it, minute cyst-like dilatations of the lymphatic involved have been found by Maitland, Daniels, and the Editor, and in these cysts coiled-up adult filariæ, sometimes dead, sometimes alive.

Filarial glandular enlargement.—In the Pacific islands great enlargement of the lymphatic glands with fibrotic changes is by far the most frequent symptom of filarial disease. The epitrochlear gland, for instance, is often affected—in Fiji in 22 per cent. of the total population.

The groin-glands are often very much enlarged, sometimes to 2 or 3 in. across, and may form permanent tumours in the groin. On section they have the appearance of an unripe pear, the central portion being fibrotic, and the peripheral glandular. The deep-seated glands—the iliac, lumbar, mesenteric, and mediastinal—may also be enlarged.

On careful dissection, live filariæ or their calcified remains may be demonstrated in the glandular substance. (Fig. 143.)

Treatment.—Usually it is inadvisable to remove these glands, seeing that, as in the case of varicose groin-glands, an incurable lymphocele might result.

Lymph scrotum (Fig. 144).—In this disease the scrotum is more or less enlarged. Though usually silky to the touch, on inspection the skin presents a few, or a large number of smaller or larger lymphatic varices which, when pricked or when they rupture spontaneously, discharge large quantities of milky, or sanguineous-looking, or straw-coloured, rapidly-coagulating lymph or chyle. In some cases 6 or 10 oz. of this substance will escape from a puncture in the course of an hour or two ; it may go on running for many hours on end, soiling the clothes of the patient and exhausting him. Usually microfilariæ can be discovered in the lymph so obtained, as well as in the blood of the patient. In a large proportion of cases of lymph scrotum the inguinal and femoral glands, either on one or on both sides, are varicose.

Treatment.—Unless inflammation be a frequent occurrence, or there be frequent and debilitating lymphorrhagia, or unless the disease tends to pass into true elephantiasis, lymph scrotum—kept scrupulously clean, powdered with boracic acid, suspended, and protected—had better be left alone.

Should it, however, be deemed expedient, for these or other reasons, to remove the diseased tissues, this can be effected easily. The scrotum should be well dragged down by an assistant while the testes are pushed up out of the way of injury. A finger knife is then passed through the scrotum, and in sound tissues, just clear of the testes, the mass is excised by cutting backwards and forwards. No diseased tissues, and hardly any flap, should be left. Sufficient covering for the testes can be got by dragging on and, if necessary, dissecting up the skin of the thighs, which readily yields and

Fig. 143.—Pedunculated groin-glands in a Fijian with double hydrocele. (*Orig.*)

These glands, containing adult ♂ and ♀ filariæ, were removed at operation. No microfilariæ were found in the blood. There were also masses of enlarged glands in right groin.

affords ample covering. It is a very common but a very great mistake to remove too little. As a rule, the wound, if carefully stitched and dressed antiseptically, heals rapidly.

In consequence of this violent interference with a large varix, of which that in the scrotum is but a part, chyluria, or elephantiasis of a leg may supervene. The patient should be warned of this possibility.

Chyluria.—When a lymphatic varix in the walls of the bladder,

or elsewhere in the urinary tract, the consequence of filarial obstruction in the thoracic duct or in the lymphatics of the urinary system, ruptures, there is an escape of the contents of the lymphatics into the urine. Chyluria is the result. If, as often is the case, it contains blood, the condition is known as hæmatochyluria.

A curious fact about this form of filarial disease is that in the Pacific islands it is practically unknown, though it is frequently met with in filariated subjects in India, China, and North Africa.

Fig. 144.—Lymph scrotum and varicose groin-glands.
(*Photo: Dr. Rennie, Foochow.*)

This disease frequently appears without warning; usually, however, pain in the back and aching sensations about the pelvis and groins—probably caused by great distension of the pre-existing lymphatic varix—precede it. Retention of urine, from the presence of chylous or lymphous coagula, is sometimes the first indication of serious trouble. Whether preceded by aching, or by retention, or by other symptoms, the patient becomes suddenly aware that he is passing milky urine. Sometimes, instead of being white, the urine is pinkish, or even red; sometimes white in the morning, it is reddish in the evening, or *vice versa*. Sometimes, while chylous at one part of the day, it is perfectly limpid at another. Great variety in this respect exists in different cases, and even in the same case from time to time, depending on temporary closure of the rupture in the lymphatic, and also on the nature of the food.[1] Chyluria is very likely to occur, either for the first time or as a relapse, in pregnancy or after childbirth.

[1] The sanguineous appearance so frequently seen in chylous urine and in other forms of filarial lymphorrhagia possibly depends in some instances on the formation of blood-corpuscles in lymph long retained in the varicose vessels, and as a result of the normal evolution of the formed elements in that fluid. In other instances it is probably caused by rupture of small blood-vessels into the dilated lymphatics: in these cases the microfilariæ appear in the urine passed during the night-time only.

Physical characters of chylous urine.—If chylous urine be passed into a urine-glass and allowed to stand, within a very short time, as a rule, the whole of the urine becomes coagulated. Gradually the coagulum contracts until, at the end of some hours, a small, more or less globular clot, usually bright red or pinkish in colour, is floating about in a milky fluid, the milky appearance of which is entirely due to suspended fat particles. Later, the fluid separates into three layers. On the top there is formed a cream-like pellicle; at the bottom, a scanty reddish sediment, sometimes including minute red clots; in the centre the mass of the urine forms a thick, intermediate stratum, milky white or reddish white in colour, in which floats the contracted coagulum. If a little of the sediment be taken up with a pipette and examined with the microscope, it is found to contain red blood-corpuscles, lymphocytes, granular fatty matter, epithelium, and urinary salts, and mixed with these in a large proportion of cases, though not in all, microfilariæ. The middle layer contains much granular fatty matter; while the upper, cream-like layer consists of the same fatty material in greater abundance, the granules tending to aggregate into larger oil globules. If a little of the coagulum be teased out, pressed between two slides, and examined with the microscope, microfilariæ, more or less active, may be found entangled in the meshes of the fibrin. According to Yorke and Blacklock, the number of microfilariæ in chylous urine varies greatly within the twenty-four hours in quite an irregular manner. If ether or xylol be shaken up with the milky urine, the fat particles are dissolved out and the urine becomes clear; the fat may be recovered by decanting and evaporating the ether which floats on the urine. Boiling the urine throws down a considerable precipitate of albumin. When the urine contains only lymph, fatty elements are absent, or are present in but very small amount. According to Young, a twenty-four-hour sample of chylous urine contains 1·8–2·6 per cent. of fat. The amount of this substance excreted is generally, though perhaps not invariably, dependent on the amount ingested with the diet.

By cystoscopy the Editor has seen in the bladder chylous vesicles which burst when fully distended, and Romiti showed by cystoscopy and ureteric catheterization that lymphatic obstruction of a limited portion of the urinary system is enough to cause chyluria.

Although chyluria is not directly dangerous to life, yet being prolonged, it gives rise to pronounced anæmia, with depression of spirits and feelings of weakness and debility, and tends to incapacitate the patient for active, vigorous life.

Lymphuria.—It would be more correct to describe a certain proportion of filarial cases passing cloudy urine as "filarial lymphuria," as Low and Wise have suggested. In these cases the abnormal element is lymph, and contains no trace of fat. Albumin is present in considerable quantity, and blood may be present as well. The chief cellular constituent is the lymphocyte. Low, who was able to investigate one of these cases shortly after death, found the lymphatic obstruction located in the kidney lymphatics, which was due to calcification of defunct filariæ.

Treatment.—The treatment of chyluria should be conducted on the same lines as that of inaccessible varix elsewhere; that is to say, by resting and elevating the affected part, and thereby

diminishing as far as possible the hydrostatic pressure in the distended vessels.

The best results are obtained by putting the patient to bed on an inclined plane with feet elevated, by restricting the amount of food and fluid, and by gentle purgation and absolute rest. Washing out the bladder with some bland substance, such as boric acid, appears to be the best form of treatment; if there is an admixture of blood, styptics may be added, as follows:

℞	Liq. adrenal. (1·1000) . .	℥i (28·42 c.c.)
	Zinc. sulph.	gr.v (0·324 grm.)
	Lot. acid. bor. ad . . .	℥x (284·17 c.c.)

To be used with an equal quantity of hot water.

Golden and O'Connor have found improvement after X-ray treatment to the kidney regions. Seven cases in all have been successfully treated.

Chylous dropsy of the tunica vaginalis, and of the peritoneum; chylous diarrhœa.—Chylous dropsy of the tunica vaginalis is not an unusual occurrence in the tropics. A fluctuating swelling of the tunica vaginalis, which does not transmit light, and which is associated possibly with lymph scrotum, with varicose groin-glands, with chyluria, or with microfilariæ in the blood, would suggest a diagnosis of this condition.

Treatment.—These chyloceles may be treated as ordinary hydroceles, either by aseptic incision or by injection. As a rule, the chylous fluid rapidly coagulates when withdrawn, but occasionally this does not occur, or it may be prevented by drawing the fluid off into a solution of citrate of potash.

If a minute portion of absorbent cotton is dipped into the receptacle, it will slowly fall to the bottom of the fluid. If the cotton is now picked up and placed under a low-power microscope, it will be found that every fibre is beset with multitudes of wriggling microfilariæ entangled by their redundant sheaths, the preparation suggesting the snake-beset Gorgon head.

Filarial orchitis with effusion into the tunica vaginalis, according to Maitland, is best treated by incision of the tunica vaginalis, turning out any clot that may be found in the sac, and stuffing the latter with iodoform gauze.

Chylous dropsy of the peritoneum and chylous diarrhœa of filarial origin are very rare.

Filarial orchitis, endemic funiculitis, and hydrocele.—The fever attending filarial orchitis—which is usually associated with lymphangitis of the spermatic cord—has been described as a separate disease ("endemic funiculitis"), but it is undoubtedly of filarial origin. It may be attended with inflammation of the scrotum, and, like ordinary elephantoid fever, resemble very closely a malarial attack, for which it may be mistaken. In cases of recurring orchitis

of filarial origin with pyrexia, adenitis and rigors, the Editor has demonstrated large numbers of microfilariæ in the tunica vaginalis at the commencement of each attack. The aspirated fluid is cloudy, contains a number of polymorph cells, occasionally erythrocytes with sheathed microfilariæ, as well as others which have cast them. In these cases the epididymis is enlarged and nodular. In sections it is possible to demonstrate dead and calcified filariæ blocking the vasa efferentia and causing extensive fibrotic changes, and it is possible that sterility is a direct result of the invasion of the genital organs by filariæ.

Recurrent attacks of filarial orchitis lead sooner or later to *hydrocele*. This condition is extremely common in association with elephantiasis of the scrotum, especially among the Polynesians. The walls of the sac are thickened and contain calcified remains of adult filariæ; the fluid is clear, straw-coloured, and usually contains microfilariæ or their remains; though, owing to the rapidity with which these embryos die in hydrocele fluid, it does not seem to be a medium particularly favourable to their prolonged existence. These hydroceles should be treated on the ordinary lines.

Makar finds that endemic filarial funiculitis, hydrocele, and epididymitis are not uncommon in lower Egypt. Although *Wuchereria bancrofti* is the primary cause of these lesions, streptococcal infections become frequently superimposed, leading to acute suppurative funiculitis which may be septicæmic or pyæmic.

The naked-eye appearances of filarial infiltrations of the cords vary as regards size, form, and number. There may be one single nodule as small as a pea, or a number of them may be strung to thickened lymphatic vessels. Sometimes lymphatic obstruction affects the vessels so as to cause lymphangiectasis and lymphatic varicoceles; it may, however, cause cystic dilatation, or "lymphocele." The spermatic veins are often the seat of chronic thrombo-phlebitis. Filarial hydrocele is associated with the formation of filarial nodules in the tunica vaginalis.

These conditions can only be treated by surgical means.

The differential diagnosis has to be made from encysted hydrocele, lipoma, spermatocele, vaginal hydrocele, syphilitic orchitis, gonorrhœal epididymitis, etc.

Septicæmia.—An acute fatal septicæmia due to *Streptococcus longus* is not an infrequent occurrence in subjects infected with *W. bancrofti*. It is suggested that the parent worm living in the lymphatic system damages the lining of the vessels, and thus prepares the ground for any pyogenic organisms which invade the lymph-stream. In damaged lymphatic tissue the streptococcus finds a favourable medium, and enters the blood-stream, with the result that septicæmia is produced.

Filarial synovitis.—Acute synovitis of the knee-joint is one of the filarial diseases. The concurrence of synovitis with filarial invasion is too common to be accidental; fibrotic ankylosis often results.

In cases where the hip-joint is affected, removal of the inflamed iliac glands draining the area appears to relieve the condition.

In severe cases the synovitis may even proceed to pus-formation, and a fatal result ensue. Surgical intervention is often indicated.

Elephantiasis

In certain districts in Cochin about 5 per cent. of the population, in Samoa about every second individual, in Huahine seven-tenths of the adult male population, are affected by this disease. In the Ellice Islands, out of a total population of 3,434, 90 are affected. In many other tropical and subtropical countries elephantiasis, if not so common as in those mentioned, is, nevertheless, very prevalent.

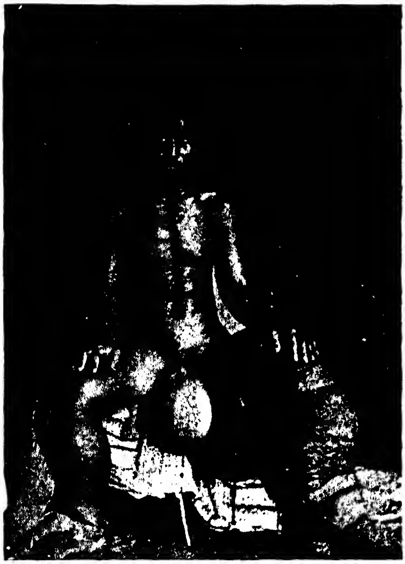


Fig. 145.—Elephantiasis of legs; scrotum and right arm also affected. (*Photo: Dr. Turner, Samoa.*)

The pathology of the disease has already been considered (p. 757).

Parts affected.—In 95 per cent. of the cases the lower extremities—either one or both—alone, or in combination with the scrotum or arms, are the seat of the disease. The foot and ankle only, or the foot and leg, or the foot, leg, and thigh, may each, or all, be involved. The scrotum is also a common situation for elephantiasis. The arms are more rarely attacked, though in Fiji elephantiasis of the arm is comparatively common: out of 47 cases the arms alone were affected in 10, both arms and legs in 6 cases. Still more rarely are the mammæ, vulva, and circumscribed portions of the integuments of the limbs, trunk, neck, or scalp involved.

The disease in any of these situations commences with a rapidly evolved lymphangitis, dermatitis, and cellulitis, accompanied by elephantoid fever. As already noticed (p. 760), O'Connor has been able to demonstrate that these attacks initiate from painful areas, known as "focal spots," and in a large proportion of cases it has been possible to demonstrate, by X-ray examination, the presence of dead and calcifying filariæ.

Golden and O'Connor (1934) reported upon irradiation by X-rays of lymphangitis and adenitis. At first merely focal spots were so treated, but later the entire leg. Out of fifteen cases four had no further attacks.

The lymphatic glands draining the affected area are generally enlarged.

There is no distinct line of demarcation between healthy and diseased skin. The implicated integuments are hard, dense, pit but slightly, if at all, on pressure, and cannot be pinched up or freely glided over the deeper parts.

On cutting into the swelling, the derma is found to be dense, fibrous

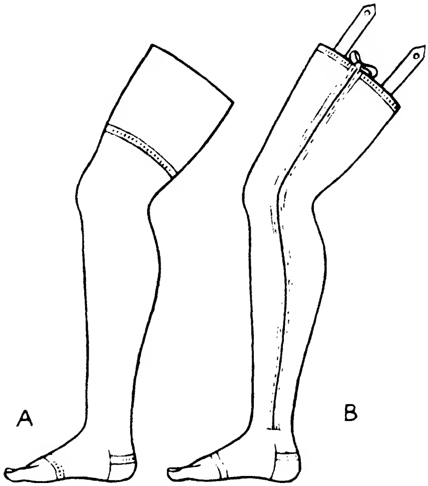


Fig. 146.—A, Plain web-elastic stocking, with foot-piece, for slight degrees of elephantiasis of leg. B, Laced form of elastic stocking, with suspenders, adjustable so as to avoid pinching. (*A, James Woolley & Sons, Manchester*; *B, Hospitals & General Contract Co.*)

and enormously hypertrophied. The subjacent connective tissue is increased in bulk, having, especially in the case of the scrotum, a yellowish, blubbery appearance from lymphous infiltration. A large quantity of fluid wells out on division of such tissues.

Elephantiasis of the legs (Fig. 145).—Elephantiasis of the lower extremities is usually, though by no means always, confined to below the knee. The swelling may attain enormous dimensions and involve the entire extremity, the leg or legs attaining a circumference, in aggravated cases, of several feet.

Treatment.—In the treatment of elephantiasis of the leg, the patient should be encouraged to persevere with elastic bandaging, massage, and elevation of the limb. Swellings in the early stages may to some extent be controlled by elastic bandages or stockings. The latter, which should be made to fit

the legs accurately, should be of some porous elastic and washable material, such as stockinette. Such a stocking (Fig. 146A) should embrace the dorsum of the foot and should accurately fit the leg to reach above the knee. Difficulty is generally experienced with the upper margin, which extends to the thigh, as it is apt to constrict or nip the limb at this point. To obviate the pressure and discomfort of tight-fitting stockings, and to accommodate the fluctuations in the size of the limb which necessarily take place, these stockings may be made to lace up at the sides (Fig. 146, B). A spiral elastic stocking made by Down Bros., on Dickson Wright's model, which can be accurately fitted to the leg and which is comfortable, airy and effective, can be recommended. Sometimes, in extreme cases, good results are got from excision of redundant masses of skin, a longitudinal strip of three or four inches in breadth by a foot or more in length being dissected off. During the acute attacks, tension may be relieved by aseptic punctures with a sharp lancet. At all times the limb must be carefully guarded from injury, and shoes and trousers worn. Slight injuries provoke inflammatory recurrences.

Knott is an advocate of prolonged and firm bandaging, which effects a gradual removal of the lymphœdema, during which time the patient obtains symptomatic relief and avoids further recurrent attacks of lymphangitis; the bandages should not be removed when an attack of lymphangitis is imminent, but the foot of the bed should be elevated. A "bandage boot" is used, consisting of a 6-inch bandage of heavy Turkish towelling, which covers the limb from behind the heads of the metatarsals to the heads of the tibia and fibula, cemented to a covering crêpe bandage by dextrin-syrup applied along the tibia, the whole being supported by narrow lateral strips. An extremely efficient stocking can be fitted on to the leg with washing canvas; it is tightened by a zip-fastener extending for one foot laterally downwards from the knee and upwards from the ankle, thus maintaining an even and readily adjustable pressure.

Various *operative* measures have been proposed, though none is entirely satisfactory. *Lanz's operation* aims at deep lymphatic drainage. A longitudinal incision is made through the fascia lata down to the femur, the periosteum of which is stripped and the bone trephined in several places; strips of fascia are then inserted into the openings thus made.

Kondoleon's operation consists also in free incision of the fascia lata and removal of large sections of the aponeurosis; the removal of this tissue assists in the anastomosis of lymph channels and veins.

Auchincloss's operation is intended to lighten elephantoid legs, and also to remove those tender focal spots whence the inflammatory lesions of filarial fever arise and to remove calcified worms. It consists of two incisions marking out a vertical strip of skin. From its ends V-shaped incisions are made diverging upwards at the upper end and downwards at the lower. An almost dangerously wide amount of skin is undermined, with considerable care, just deep to the corium.

Elephantiasis of the scrotum.—Elephantiasis of the scrotum or "scrotal tumour" as it is sometimes called, may attain an enormous size: 10, 15, 20 lb. are common weights for these tumours, and 40 or 50 lb. is by no means uncommon. The largest recorded weight is 224 lb.

Anatomical characters. These tumours consist of two portions (Fig. 147): first, a dense rind of hypertrophied skin (A, *e*), thickest towards the lower

part and gradually thinning out as it merges above into the sound skin of the pubes, perineum, and thighs; second, enclosed in this rind, a mass of lax, blubbery, dropsical, areolar tissue in which testes, cords, and penis are embedded. The shape of the tumour is more or less pyriform. The upper part, or neck, on transverse section (B) is triangular, the base (B, *k*) of the triangle being in front, the apex (B, *j*)—usually somewhat bifid from dragging on the gluteal folds—towards the anus, the sides (B, *h*) towards the thighs. In the latter situation the skin, though usually more or less diseased, is, from pressure, softer and thinner than elsewhere, tempting the surgeon to utilize it for the formation of flaps—not always a wise proceeding. The penis (A, *a*, B, *f*) always lies in the upper and fore part of the neck of the mass; it is firmly attached to the pubes by the suspensory ligament. The sheath of the penis is sometimes especially hypertrophied, in some cases standing out as a sort of twisted ram's-horn-like projection on the anterior surface of the tumour; this, however, is unusual. Generally the sheath of the penis is incorporated in the scrotal mass, the prepuce being dragged on and inverted so as to form a long channel leading to the glans penis and opening (A, *l*) half-way down, or even lower, on the face of the tumour. The testes (A, *c*), buried in the central blubbery tissue, usually lie towards the back of the tumour, one on each side—in large tumours generally nearer the lower than the upper part. They are more or less firmly attached to the under-part of the scrotum by the hypertrophied remains of the gubernaculum testis (A, *d*)—a feature to be specially borne in mind by the surgeon. As a rule both testes carry large hydroceles with thickened tunicæ vaginales. The spermatic cords also (A, *b*; B, *g*) are thickened and greatly elongated.

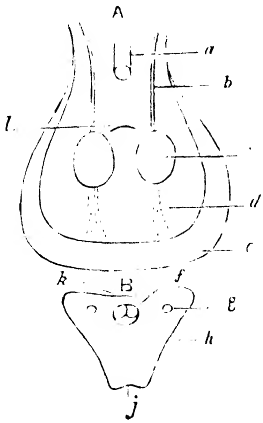


Fig. 147.—Diagram of anatomy of elephantiasis of scrotum. (For references, see text.)

The arteries which supply these enormous growths are of considerable size; the veins, too, are very large, and, as they permit regurgitation of blood from the trunk, are apt to bleed freely.

Treatment preliminary to operation.—If the tumour is of considerable size the patient should keep his bed for at least a week before operation, the mass being suspended so as to drain it of fluid and blood. It is thus rendered lax, and the operator is enabled to ascertain by palpation the position of the testes and, if such chance to be present, of hernia—a not very unusual complication. The possibility of undescended testes should not be overlooked. The choice of anæsthetic is important: it should be spinal when possible, reinforced with gas and oxygen. The patient should not be kept long in bed prior to the operation, for when the mass is supported, the fluid drains upwards and invades the tissues to be used for flaps, and the palpable edge of the elephantoid skin is obscured.

Operation.—The patient should be placed in the lithotomy position. The scrotum should be drawn down as far as possible, and elastic webbing applied over the mass so as to expel the blood; a stout rubber cord is wound round the neck of the tumour, over the pelvis, and firmly secured. A vertical

incision is made commencing in the middle of the symphysis pubis, and extending as far as the aperture leading to the penis. The penis is exposed, separated and the penal artery ligatured. It should be borne in mind that the prepuce and skin of the sheath of the penis have been pulled down over the glans and form a skin-lined tube from the gland to an opening on the front of the tumour, and while the skin of the prepuce and the sheath and even the frænum may be elephantoid, the skin of the glans is normal. At this point, a sound is passed, and left in to prevent subsequent injury to the urethra. The vertical incision is now continued round the scrotum right round to the back of the perineum, and the scrotum is thus divided into two halves. The testicles and cords are now separated from the blubbery mass, the hypertrophied gubernacula being divided, surrounded with gauze and placed on one side. At the base of each half of the scrotum clamps are fixed, care being taken that these clamps are well to the proximal side of all diseased tissue. Each half of the scrotum is then cut away, distal to the clamps, and through healthy tissue. Every visible blood-vessel is secured and tied and the clamps very gradually loosened. The skin in the upper and inner aspects of the thigh is undermined as much as necessary and brought together over the testicles. Thiersch skin-grafts may be applied to the penis, and give good cosmetic and functional results, and if done at the time of the operation will take on in 100 per cent. of cases. It is a good procedure to tie in a catheter till healing has taken place.

Complications which may ensue are severe hæmorrhage, and injury to spermatic cords, urethra or rectum. Postoperative retention of urine is often very troublesome. Stricture of the urethra and the supervention of elephantiasis of a previously unaffected leg have also been recorded.

The mortality from these formidable-looking operations, if they are carefully done, is small, and need not exceed 5 per cent.

Knott insists that the most important factor is the position of the patient on the operating table. If the patient is placed on a horizontal table with his legs over the sides supported by chairs, the mass can be rolled to the opposite side, and this does away with the need of a rubber tourniquet.

Early cases of elephantiasis of the scrotum who are still subject to attacks of fever with lymphangitis and cellulitis which involves the skin of the penis and scrotum, require to be handled in a different manner. In these cases enough skin should be saved to cover the testes, and one should remember that the more skin taken, the less likelihood there is of a recurrence.

Elephantiasis of the arms.—This is comparatively rare. Allowing for the differences between the upper and lower extremities as regards gravitation of fluids, the symptoms and pathology of elephantiasis of the arms are the same as those of elephantiasis of the legs. Beyond the judicious employment of massage and elastic bandaging, little can be done in the way of treatment. (Fig. 148.)

Elephantiasis of the vulva and mammæ.—Elephantiasis of the vulva (Fig. 149) and mammæ (Fig. 150) is still rarer. Where growth has become inconveniently large, the diseased tissues should be removed. Instances are on record in which the integuments of the mammæ have become so thickened, heavy, and elongated that the organ has descended to the pubes, and even to the knee. One such tumour weighed 21 lb. after removal. Tumours of the labia or

of the clitoris, similarly, may attain a great size—8 or 10 lb., or even more.

Elephantiasis of limited skin areas.—Corney stated that pedunculated elephantoid tumours, springing from the groin or from the anterior surface of the thigh, were not uncommon in Fiji. One such tumour which he removed weighed 20 lb. Daniels saw, both in Fiji and in Demerara, several cases of this description.

Fig. 148.—Elephantiasis of right arm and hand in a Fijian. (*Orig.*)

Filariasis and elephantiasis due to Filaria malayi.—It is claimed that the disease produced by this species differs in some respects from that produced by *Wuchereria bancrofti*, a fact that has recently been recognized from the work of Poynton and Hodgkin. *F. malayi* is endemic in Malaya in the low-lying riverine areas, where the rivers run into the sea. The microfilaria-rate in the natives living in the vicinity of swamps is 9·3 per cent., which is about the same as the elephantiasis rate ; as in the case of *W. bancrofti*, the liability to infection increases with age.

Adenitis is the earliest detectable lesion and takes the form of enlarged glands; inflammation of the groin-glands is frequently seen in children. Lymphangitis is also a familiar phenomenon and has a

Fig. 149.—Elephantiasis of vulva. (*Photo: Dr. Walter H. B. Macdonald.*)

Fig. 150.—Elephantiasis of mammæ; left leg and foot also affected. (*Photo: Dr. Davies, Samoa.*)

definite periodic character which is regarded (possibly correctly) as negativing its streptococcal origin, but which is more probably correlated with periodic parturition of the female worm. Elephantiasis due to *Filaria malayi* is of a low-grade character, is invariably confined

to the legs, and is usually unilateral. There appears to be great variability in the rate at which elephantoid lesions are produced. In highly infected areas it is seen in comparatively young people, especially in males, though it is typically a disease of adult life. Microfilariæ are, as a rule, found only in 5 per cent. of cases.

Medicinal treatment of filariasis.—It must be confessed that, at present, there is no drug known to be specific for *W. bancrofti*.

Anderson in British Guiana found that certain antimony compounds, such as the colloidal preparation known as "Oscol stibium" (0·5–1 c.c.), given intramuscularly every other day, definitely inhibit the number of circulating microfilariæ, and so does sodium-antimony tartrate, if given intravenously in therapeutic doses; but the effect is not permanent. In septic conditions, vaccines are of distinct benefit, while sulphanilamides, especially prontosil rubrum and proseptacine, are specially indicated under modern conditions.

Prophylaxis of filarial disease.—The prevention of filarial disease resolves itself into antimosquito measures and protection from mosquito-bite. Unprotected wells, tanks, or stagnant pools must not be permitted in the neighbourhood of dwelling-houses. All vessels used for storing water should be emptied at least once a week. The mosquito-net is indispensable in filarial as well as in malarial countries. In the Pacific Islands, especially in the Gilbert and Ellice group, a very considerable reduction of filarial incidence has taken place following upon O'Connor's recommendation. He advised cutting down the thick undergrowth, thus giving passage to the Trade Winds which blow away the special mosquitoes (*Aëdes variegatus*), and destroying their breeding-places. Burning empty coconut shells and filling up holes and cavities in the trunks of the coconut trees has been beneficial.

Sweet and Pillai record a successful campaign waged against the intermediary mosquito of *Filaria malayi*—*Mansonioides annulifera*, and the plant *Pistia stratiotes*; this latter they succeeded in clearing from North Travancore, with the consequent elimination of filariasis from that area.

The subjects of filariasis should be regarded as dangers to themselves and to the community, and be compelled to sleep under mosquito-nets.

II. FILARIASIS DUE TO LOA LOA

History and geographical distribution.—The embryonic form (microfilaria diurna), which closely resembles microfilaria bancrofti, was described by Manson in 1891; the patient from whom the specimen of blood was derived had formerly had an adult *Loa loa* in his eye. Later, association was established between *L. loa* and the disease known as Calabar swellings, and also between that disease and microfilaria diurna.

Loa loa is widely distributed in West Africa from Sierra Leone to Benguella, and is especially common in the Cameroons and on the Ogowe River; its distribution is, however, mainly confined to the coastal plains and follows the course of the Congo and its tributaries to a point about 1,500 miles from its mouth (Map VI).

Ætiology.—A minute description of the adult loa is given in the Appendix, p. 957. Here it suffices to say that it is 30 mm. or more in length, the female being, as a rule, considerably longer than her partner (Fig. 151.). The cuticle is embossed with numerous characteristic protuberances.

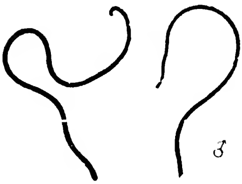


Fig. 151.—*Loa loa.* Nat. size.

Structure of the embryonic form.—Microfilaria loa (= diurna) is very similar in size (298 μ by 7·5 μ) and structure to microfilaria bancrofti. Like the latter, it is enclosed within a "sheath," its tail is pointed, and it has the same V- and tail-spots. (Fig. 128, *2*, p. 744.)

The periodicity is the exact reverse of that of microfilaria bancrofti, for the embryos appear in large numbers in the peripheral blood during the daytime and disappear at night. The periodicity is, in fact, *diurnal* (Chart 28).

The respective periodicities are very characteristic—more so, apparently, in the case of microfilaria loa than in that of microfilaria bancrofti; for whereas by inverting the sleeping habits of a subject of *F. bancrofti* infection it is easy to invert or disturb the periodicity of the microfilariæ, this has not been done easily in the case of microfilaria loa, although several experiments have been made. Probably it takes place gradually as for instance, when the patient travels round the world.

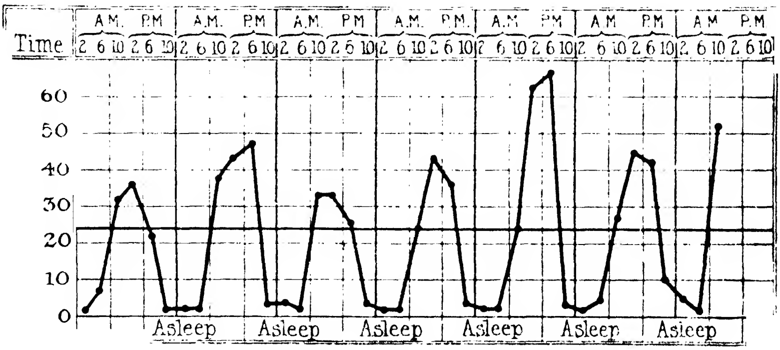


Chart 28.—Diurnal periodicity of microfilaria loa (mf. diurna). (*Orig.*)
The numbers in the first column are those of the microfilariæ per 16 c.mm. of blood.

Life-history.—In early editions of this work Manson called attention to the mangrove fly, *Chrysops dimidiata* (Fig. 328, p. 1002), as a possible intermediary, on account of its diurnal and blood-sucking habits and local distribution. This conjecture Leiper, and later Kleine and Connal, have

ascertained to be well founded. Development takes place in the thoracic muscles and fat-body of *C. dimidiata* and *C. silacea*.

It would appear that after the larva has entered the human body, development is very slow, and that probably full maturity is not attained until after several years. In many cases the parasite does not show itself until three, four, or four and a half years after the patient has left the endemic area. In one case the parasite was extracted from the eye thirteen years after the patient had left Africa; in another the worm or worms appeared at irregular intervals during fifteen years. Manifestly it is long-lived. An interesting and suggestive evidence of slow development is that, while the immature active worm is often seen in children, the embryonic form in the blood is found as a rule only in adults, it may be as long as seven years from the time of the original infection.

This slow development of *L. loa* would seem to account for the very frequent failure to find the microfilariæ in the blood in cases from which mature parasites have been extracted, a circumstance which has been brought forward as an argument against the theory that the diurnal microfilaria is really the offspring of *L. loa*.

As yet it is impossible to estimate accurately the number of adult loas present in any given infection, although in advanced cases some idea of this might be got from the number of microfilariæ in the peripheral blood. As a rule, it is safe to conclude that the particular loa that may show itself about the eye or elsewhere is only one of many. Thus, in 1903, Brumpt, at the post-mortem of a negro whose blood contained microfilariæ, found in the tissues of the heart five adult worms. Four of these were cretified, but the fifth was alive and contained embryos similar to those in the blood.

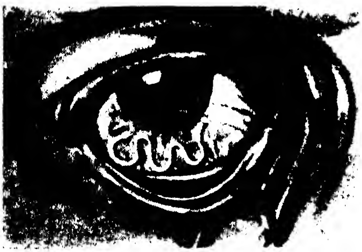


Fig. 152.—Loa loa in the eye. (*After Fülleborn.*)

Pathology. — As already stated, *L. loa*, during the period of its growth and development in man, makes frequent excursions through the subdermal connective tissues. It has been noticed very often beneath the skin of the fingers, and it has been excised from under the skin of the back, from above the sternum, from the left breast, the lingual frænum, the loose skin of the penis, the eyelids, the conjunctiva, the anterior chamber of the eye, and also the scalp. The parts most frequently mentioned are the eyes, and, although the worm may attract more attention when in this situation, it does seem as though it had a decided predilection for the eye and its neighbourhood (Fig. 152). A patient of Manson's once stated that the average rate at which a loa travelled was about an inch in two minutes. Both he and others have observed that warmth, such as when sitting before a fire, seems to attract them to the surface of the body. Chesterman on the Congo reports finding live adult worms in 10 per cent. of all cases operated upon for hernia, elephantiasis, etc. Cretified worms, too, are frequently encountered. Whether alive

or dead this parasite evokes a high eosinophile response, and an increase of these cells to 30, 40 and even higher percentages is commonly met with in Europeans who have resided in the endemic districts in Southern Nigeria.

Symptoms.—As a rule, the migrations of the parasite give rise to no serious inconvenience, but they may cause prickings, itching, creeping sensations, and, occasionally, transient œdematous swellings (Calabar swellings) in various parts of the body. When the parasite appears under the conjunctiva it may cause a considerable amount of irritation and congestion; there may be actual pain even, associated with swelling and inability to use the eye and, perhaps, tumefaction of the eyelids (Fig. 153). Should a loa wander into the vicinity of such a situation as the rima glottidis, or the urethra, the consequences might be serious. Great pain is sometimes caused by the wanderings of this parasite in that region as well as in the neck of the bladder. Occasionally, too, as Chesterman has recorded, the death of the parent worm may cause a localized abscess to form in the groin or axilla, and the Editor has seen two of these

Fig. 153.—Calabar swelling of right eye. (*Orig.*)

CALABAR SWELLINGS

Under this name Thompstone originally described certain fugitive swellings which are of frequent occurrence in natives and Europeans alike in parts of tropical West Africa. The swellings are about the size of half a goose egg, painless, though somewhat hot both objectively and subjectively, not pitting on pressure, and usually disappearing in about three days. They come suddenly and disappear gradually, and occur in any part of the body. One swelling occurs at a time, but recurs at irregular intervals and, it may be, for many years after the patient has returned to Europe. In some instances the swellings seem to be induced by the rubbing provoked by the irritation accompanying the presence of a loa just under the skin; in other instances they develop spontaneously. When occurring in the hand, or about the forearm, they may give rise to a sensation of powerlessness and soreness, as if the part had received a blow. They never suppurate. (Fig. 154.)

Although in a large proportion of cases *L. loa* embryos cannot be found, in a number of others either the parent worm has shown itself in the eye or its microfilariæ have been detected in the blood.

The latter circumstance, together with the geographical feature of the endemicity of these swellings and their clinical characters, makes it practically certain that they are produced by *L. loa*. Manson believed that the swelling might be caused by the emission of her larvæ by a parent loa into the connective tissue, but it was recognized by Fülleborn that these swellings represent an allergic reaction on the part of the tissues in response to the filarial toxins.

The recurrence of Calabar swellings on the arm or leg appears to give rise to induration of the fascia and connective tissue in the vicinity of the tendon-sheaths. In two cases the Editor has observed permanent circular cyst-like swellings which may cause pain on muscular movement. Apparently these swellings are attached to the tendon-

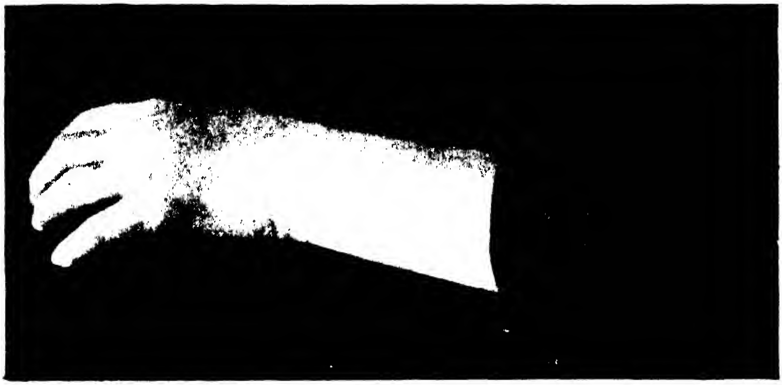


Fig. 154. Calabar swelling on dorsum of hand in a European lady from the Congo. (*Orig.*)

sheaths and muscular aponeuroses. Solid œdema of one leg persisting for six weeks has been observed in a European from West Africa who had been infected for a number of years: hydroceles also have been noted by the Editor (Fig. 155.)

Urticaria and *dermatitis* of a particularly irritating form are sometimes found in filaria cases. The dermatitis, which can be controlled by heliobrom (*see* p. 787), is analogous to that found in onchocerciasis. As in infection with *W. bancrofti*, multiple intramuscular abscesses, due to staphylococci or streptococci, and even purulent infections of the hip-joint may be found in association with *Loa loa*.

Treatment.—Calabar swellings are notoriously difficult to treat effectively. The irritation can best be allayed by evaporating lead lotion, or by heliobrom in alcohol. Fairley has recently employed a desensitization method with increasing strengths of *Dirofilaria* antigen, commencing with 0·5 c.c. of the extract in normal saline, and gradually

increasing the amount to 5 c.c. or more, with some apparent measure of success. De Choisy and others have asserted that the infection may to some extent be controlled by injections of antimony, e.g., tartar emetic; and it is claimed that in some cases Calabar swellings can be successfully treated by employing anthiomaline intravenous injections every other day, employing 3 c.c. of a 6-per-cent. solution.

III. HUMAN ONCHOCERCIASIS

History and geographical distribution.—*Onchocerca volvulus* was originally discovered by a German medical missionary in negroes of the Gold Coast. The contained parasite was named *Filaria volvulus* by Leuckart in 1893. Blanchard, in 1899, demonstrated the parasite lying in a lymphatic space in a tumour. It occurs sporadically throughout the whole of the Congo basin, but especially on the Oellé, Kibali, and Itimbiri rivers. It has been observed in Nigeria (Best and Parsons), in the Cameroons (Fülleborn), in Senegal and French Guinea (Clapier), in Uganda (Cook), in Kenya (Kakamega—Harley-Mason), in Tanganyika, in Nyasaland, and in the southern Sudan (Bahr-el-Ghazal.—Bryant) (Map VI).

Fig. 155.—Hydrocele and solid œdema of right leg in *L. loa* infection from West Africa. (*Editor's case.*)

In 1915 Robles described *O. volvulus* as being of common occurrence in Guatemala. Calderon (1920) has defined the endemic zones as being in the departments of Sacatapéquez, Escuinthla, and Solola, at an altitude of 2,800–3,600 ft. It is suggested that the parasite was imported by negro slaves from Jamaica, though Brumpt regards it as a distinct species—*O. cæcutiens*, "the blinding filaria"—mainly on account of its association with a curious punctate keratitis, minor distinctions in the morphology of the male parasite, the predilection of the tumours for the head, and the endemic zone of the disease at an altitude of 600–1,200 metres. De la Torre has described onchocerciasis as being common in Mexico, over 15,000 cases in the State of Chiapas and 5,000 in Oaxaca being known. Now Strong, Sandground, and Bequært (1934) in their monograph on onchocerciasis in

Central America, have confirmed the morphological identity of *O. volvulus* and *O. cæcutiens*. In Guatemala onchocerciasis occurs endemically in those districts in which coffee is grown, from 2,800–3,000 ft., especially in the Indian population.

Ætiology.—The worms are white in colour and filiform, tapering at both ends. They vary considerably in length, the female, as in all the filariæ, being much the longer (35–40 cm.). At least four males and two females are present in every tumour. The unsheathed embryos measure about 300 μ in length.[1]

Life-history.—Embryos, presumably those of *O. volvulus*, have been found in the peripheral circulation by Fülleborn, Simon, Ouzilleau, and Rodenwaldt. The microfilariæ occur round the periphery of the tumours, and are ingested by the jinja-fly (*Simulium damnosum*), in the thoracic muscles of which they undergo a development similar to that of *W. bancrofti* (Blacklock). In South America the definitive hosts are *Eusimulium aridum* (*metallicum*), *E. ochraceum*, and *E. mooseri*.

Gibbins and Lœwenthal have now shown that in Victoria Nyanza district of Uganda the distribution of cutaneous onchocerciasis coincides with that of *Simulium damnosum*.

Fig. 156.—Onchocerciasis from the Congo.
(*Dr. C. C. Chesterman.*)

Pathology and symptoms.—*O. volvulus* is found in peculiar subcutaneous fibrous tumours, the size of a pea to that of a pigeon's egg. The same patient may present one or several of these tumours (Fig. 156). The regions of the body most frequently affected are those in which the peripheral lymphatics converge. Thus the tumours are usually found in the axilla, in the popliteal space, about the elbow, in the suboccipital region, and in the intercostal spaces. In their incipient stages they

[1] Macfie and Corson report that in the Gold Coast natives microfilariæ are commonly encountered in sections of the skin. The embryos, they believe, are referable to a new species, *Agamofilaria streptocerca* (*see* p. 965), distinguishable from those of *O. volvulus*. The presence of this filaria is associated in some with a lichenoid condition of the skin.

are the seat of very considerable pain. Periodic recurrences of symptoms are attributable, according to native belief, to the lunar cycle, occurring almost every fifteen days. In the South American form the occipito-frontal and temporal regions were noted to be most usually affected. Strong found in Ste. Emilia, Guatemala, 54 per cent. of the inhabitants infected with *O. cæcutiens*.

The tumours are situated on the head usually the scalp measuring 6–20 mm. rarely as much as 30 mm. In this situation the tumours may cap the skull and from them the adult worms may be obtained entire by digesting the tissues with papaya juice or papaine in 0·2-per cent. HCl. The tumours are never adherent to the surrounding structures and can be easily enucleated. They are formed of a dense mass of connective tissue, which enwraps the parasites and encloses small cyst-like spaces filled with a greyish viscous substance consisting almost entirely of microfilariæ. The position of the adult worms within these tumours is very remarkable. The greater length of the coiled-up bodies of the females is embedded in the connective stroma ; consequently they cannot be extracted unless in fragments.

Though most commonly found in adults of mature years, Strong has seen *volvulus* tumours in a child of two months, and he has found that they often give rise to neoplasms. Sometimes, however, especially in Europeans, the embryos may exist in large numbers in the skin without any ascertainable nodules.

Robles reports that tumours of the scalp may produce epileptiform attacks in Colombia, due to perforation of the cranium by tumours of the periosteum. Erysipelatoid skin-rashes (known as "*Erisepela de la costa*,") are common in the South American form.

Lymphatic enlargement of the scrotum, hydroceles and enlarged testes have been noted by Dyce Sharp in patients infected with *O. volvulus*, while the embryos can be demonstrated in hydrocele fluid, as well as in œdematous lymphatic tissue. On the Congo, Ouzilleau has described elephantiasis of the scrotum and the legs in association with this parasite, and Chesterman has confirmed these observations on the Congo. As in *W. bancrofti* infections, localized abscess formation also occurs in *O. volvulus*, and several dead female worms have been removed from a number of abscesses. The elephantoid scrotum due to *O. volvulus* is convoluted like a brain, with the subcutaneous tissue more solid and less œdematous than that commonly attributed to *W. bancrofti*, and the embryos of *O. volvulus* are found in the skin.

Déjou (1939) has described acute arthritis in onchocerciasis in French West Africa. Microfilariæ can be demonstrated in the synovial fluid obtained by joint puncture, and it should be examined soon after withdrawal. In these cases filarial nodules can be found in the cruro-inguinal region, in the popliteal spaces, and on the costal margins.

Skin symptoms.—It is a very interesting point that a dermatitis (xeroderma) or lizard skin (Rodhain and Dubois) is commonly associated with *O. volvulus* infections, especially in Europeans. The skin affection is described by some as *lichenoid* and is more easily visible on the back (Fig. 157). It is usually seen in South American cases, but

shows up much better in Europeans than in dark-skinned natives. The skin is thickened as well as wrinkled. Fülleborn has described these cases in German colonists from Mexico. This is the condition termed *lichen* by Macfie and Corson in West Africa, and *scleroderma* by Ouzilleau.

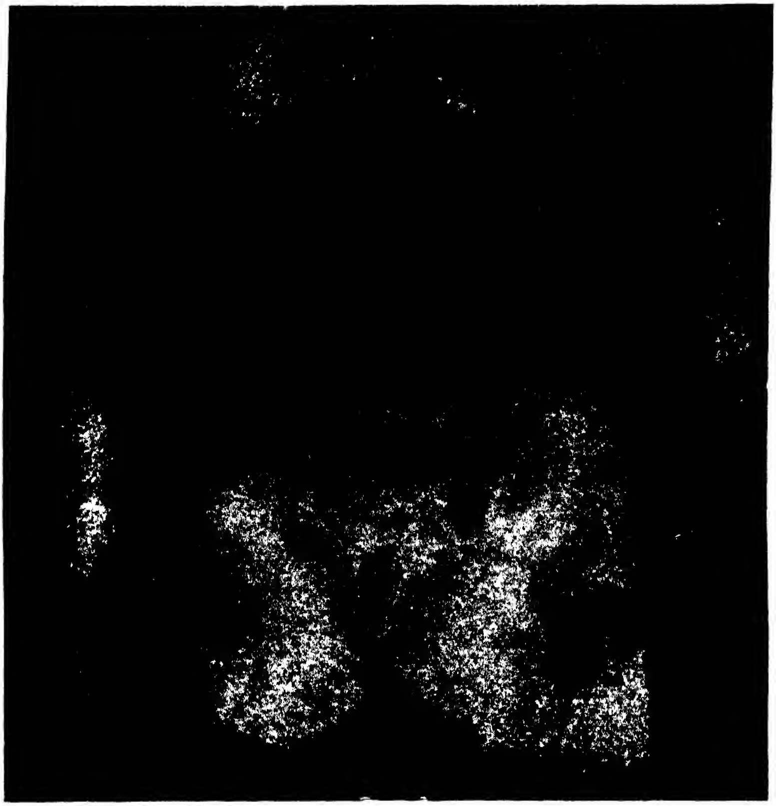


Fig. 157.—Lichenoid eruptions of onchocerciasis. (*After Fülleborn.*)

Recurrent inflammations of the skin, when on the face, often result in enlargement of the pinna of the ear.

In these there is a definite dermatitis with discoloured patches of skin on the neck and back, with xeroderma, especially of the elbows. Associated with these skin changes the patient experiences terrible pruritis, especially at night-time.

Usually several onchocerca nodules can be found in the deep subcutaneous fascia, and when excised, the adult worms can be

demonstrated, as can the living embryos, by teasing a snippet from the surrounding skin (Fig. 158). Quite commonly the patients suffer from photophobia and some aberrations of vision. There is usually an eosinophilia of about 35 per cent.

Eye lesions.—In 1918 Pacheco Luna suggested that *O. volvulus*, in its migrations through the body, was responsible for a peculiar form of keratitis punctata commonly found in Guatemala. Calderon suggested that it produces lesions of the iris and cornea as well. Similar eye lesions have been described amongst the Congo negroes by Hissette. Photophobia, xerosis, and impaired vision result, or the

Fig. 158.—Photomicro. of microfilaria of *O. volvulus* in subcutaneous tissue. Note absence of tissue reaction.
(*Dr. P. H. Martin, Editor's case.*)

pupil may become obliterated and complete blindness ensue. Interstitial keratitis, keratitis punctata, and uveitis associated with pannus are other lesions which have been described. It is to be noted that keratitis punctata is not regarded as specifically characteristic, but as an epiphenomenon (Fig. 159). In the acute stage eye lesions are associated with erysipelas of the face and ear, neuralgia, and pyrexia. The chronic form is characterized by œdema of the face and a greyish pigmentation of the skin. The skin symptoms have periods of exacerbation every fifteen days. Further studies have now been made by Strong and Sandground in Guatemala (1934).

Silva has found microfilariæ in the choroid and the posterior two-thirds of the cornea in sections of the eyes, and these findings could be confirmed by seeing microfilariæ actually creeping on the

corneal surface, and they can be found in the anterior chamber and in the iris, as they are phototropic and are visible by the corneal microscope, as recorded by Boase (1935) and Mexican ophthalmologists. Entropic vision of the embryos crossing the visual fields is by no means uncommon. The pannus of onchocerciasis ultimately causes blindness, and also pigmented choriodo-retinitis, as described by Hisette. Unfortunately, removing the operable tumours does not eradicate the disease, because new ones form. In Mexico City, where the disease cannot spread, microfilariæ can still be found in the skin years after the primary operation. The eye lesions are late manifestations of onchocerciasis, and are rarely seen in children.

It is also apparently true that the greater the distance between the eyes and the localization of the adult parent filariæ, the longer will be the delay in the development of eye lesions.

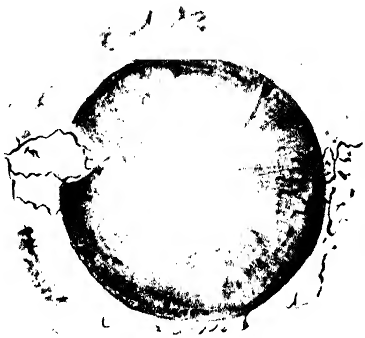


Fig. 159. Ocular onchocerciasis from the Congo, showing punctate keratitis and lateral formation of pannus. (*Hissette.*)

Diagnosis.—The diagnosis is made by snipping off a piece of skin with forceps near an onchocerca nodule, placing it in saline solution for 15 minutes at 37° C., centrifuging and then pipetting off the bottom layer with the microfilariæ which have escaped from the tissues. The embryos are definitely thermotactic, and are attracted by heat to the surface of the skin : thus demonstration of the embryos is best effected by placing hot fomentations on the skin, and then taking off shavings by means of a Thiersch razor. When these are placed in warm physiological saline solution, the embryos can be easily detected. The only practical measure to alleviate pruritis is *heliobrom* (Dibromotannic urea) 10 per cent. in spirit—*vini rectificati* (T. Teichgræber, Berlin), applied to the skin at night.

Intradermal tests.—These tests have been carried out by Fülleborn and by Rodhain and Dubois with dirofilaria antigen (*see* p. 755). The results have not been as satisfactory as in other filarial infections.

Serological reaction in onchocerciasis.—Van Hoof has employed a complement-deviation test for onchoceriasis, based upon the same principles as other similar tests in filariasis and he considers that it has done much to remove uncertainties regarding the pathogenic action of this parasite.

In the preparation of the antigen, the tightly-packed mass of adult parasites is retained when dissected out of the cyst. The filariæ are then cut into thin slices and placed in a desiccator over sulphuric acid, and when

dry they are extracted with ether at 25° C.—a process which occupies several days—and are subsequently dried and extracted with alcohol for ten days. The best extracts have an antigenic titre of 1 : 25. It is claimed that the test when put up by the Calmette-Massol technique is so specific that neither *Loa loa*, *A. perstans*, nor intestinal helminths are able to vitiate it. The antibodies thus demonstrated are present in serum, cerebro-spinal fluid, synovial fluid and œdematous exudates.

The observations so far made on the positive reactions in this test are in favour of the view that certain forms of elephantiasis in the Congo are manifestations of onchocerciasis.

Treatment.—In the African form the tumours appear to be painless, and may be removed by excision. In the South American form, removal of the tumours under cocaine anæsthesia is said to be followed by an improvement in the ocular conditions within a week or thereabouts. Adams (1938) stated that in the case of a European from the Katanga province of the Congo intravenous injections of neostibosan arrested progress of the corneal opacities, but in a comparable case observed by the Editor, no improvement was noted, so that antimony therapy had to be discontinued. Hoffmann states that atebrin in large doses has achieved a reputation in Mexico as a valuable therapeutic agent.

IV. DRACONTIASIS

Synonym.—Guinea-worm.

Geographical distribution.—This important parasite, *Dracunculus medinensis*, is found in certain parts of Africa and India, and appears to have been imported into America. In Africa it occurs in the Valley of the Nile, Lake Chad, Bornu, and West Africa; it has been observed in Uganda, but not in the Congo basin. It is also found in Persia, Turkestan, Arabia, and in a very limited part of Brazil (Feira de Santa Anna). Formerly it was supposed to be endemic in Curaçao, Demerara, and Surinam. Dracunculus is not equally diffused throughout this extensive area; it tends to special prevalence in limited districts, in some of which it is excessively common. In parts of the Deccan, for example, at certain seasons of the year nearly half the population is affected; and in places on the West Coast of Africa nearly every negro has one or more specimens about him. In Europe, guinea-worm is seen only in natives of, or in recent visitors from, the endemic areas. In North America, according to Chitwood, it has been found in the silver fox (*Vulpes fulva*), the racoon (*Procyon lotor*), and the mink (*Putorius vison*), but never in man. In Asia and Africa the parasite is widespread amongst the carnivora.

Ætiology. *The parasite.*—The male worm has only rarely been found (*see* p. 967). The female measures about 32·5 cm. to 1 m. 20 cm. in length by 1·5 mm. in diameter. The embryos are somewhat flattened, with a tapering tail, and measure 0·5–0·75 mm. in length by 0·017 mm. in breadth.

Life-history.—The embryos of *D. medinensis* are shed into water and, swimming about actively, enter the body-cavity of a fresh-water crustacean, *Cyclops quadricornis*, or an allied species, in which it develops until a length of 1 mm. is attained. (For details, *see* Appendix, p. 968.)

Mode of infection.—The metamorphosis of *D. medinensis* in cyclops was discovered by Fedchenko in Turkestan and subsequently confirmed by Manson in England; but, owing to the colder climate of this country, the metamorphosis takes longer to complete—eight or nine weeks, instead of five weeks as in Turkestan. Fedchenko supposed that the cyclops, containing the larvæ of the guinea-worm, on being swallowed by man in drinking-water, was digested, and that the parasite, being then set free, worked its way into the tissues of its new and definitive host.

Later, Leiper showed that when an infected cyclops is transferred to a 0·2-per-cent. solution of hydrochloric acid it is immediately killed, but the larvæ, so far from being destroyed, are aroused to great activity, and eventually escape into the fluid, in which they swim freely. From this he conjectured that under natural conditions man becomes infected through the ingestion of cyclops containing these worms, the gastric juice acting on cyclops and larva in the same way as the hydrochloric acid in his experiment. In order to prove this he fed a monkey on bananas concealing cyclops which had been infected for five weeks, and which contained fully-developed larvæ. Six months later, when the monkey died five worms were found in its connective tissues, all possessing the anatomical characteristics of *D. medinensis*.

The evidence is now fairly complete that the life-span of the female dracunculus before she appears on the surface of the body, extends to about one year. It is not to be supposed that every species of cyclops is an effective intermediary; if this were the case, guinea-worm infection would have a much wider geographical range.

Pathology and symptoms.—The parasite, on attaining maturity, makes for the legs and feet; these are the parts of the human body most likely, in tropical countries, to come in contact with puddles of water, the medium in which cyclops—the intermediary host—lives. The water-carriers in India are very subject to guinea-worm, which, in their case, is prone to appear on the back—that is, the part of the body against which the water-skin lies when being carried. One might interpret this by suggesting that the mature guinea-worm, conformably to her instinct, seeks out that part of the body most in contact with water, which, in the case of the Indian water-carrier, is his back.

Occasionally the guinea-worm fails to pierce the integument of her host; sometimes she dies before arriving at maturity. In either case she may give rise to abscess; or she may become cretified, and in this condition may be felt, years afterwards, as a hard convoluted cord under the skin, or be discovered on dissection.

The haunt of the female guinea-worm is the connective tissue of the limbs and trunk. When mature, and prompted by instinct, she proceeds to bore her way through this tissue, travelling downwards. In 85 per cent. of cases she presents in some part of the lower

extremities. Occasionally she presents in the scrotum or on the sole of the foot (Fig. 160); rarely in the arms; exceptionally in other parts of the body, or even in the head. In a proportion of cases the appearance of the worm at the surface of the body is preceded by slight fever and urticaria; the onset of the skin eruption is generally at night, before the blister or other localizing signs are noted. Arrived at her destination, the female worm pierces the derma. In consequence of some irritating secretion, a small blister, containing, as a rule, numerous embryos, now forms and elevates the epidermis over the site of the hole in the derma. The irritation due to this act causes a burning sensation and induces the patient to immerse his foot in water. By and by the blister ruptures, disclosing a small superficial erosion $\frac{1}{2}$-$\frac{3}{4}$ in. in diameter. At the centre of the erosion, which sometimes quickly heals spontaneously, a minute hole, large enough to admit an ordinary probe, is visible. Occasionally, when the blister ruptures, the head of the worm is seen protruding from this hole; as a rule, however, at first the worm does not show. If now we douche the neighbourhood of the ulcer with a stream of cold water expressed from a sponge and, as the water falls, watch the little hole in the centre of the erosion, we shall see in a few seconds a droplet of fluid—at first clear, later milky—well up through the hole and flow over the surface. Sometimes, instead of this fluid, a small, beautifully pellucid tube, the uterus, about 1 mm. in diameter, is projected through the hole in response to tne stimulus of the cold

Fig. 160.—Guinea-worm emerging from sole of foot. (*Editor's case.*)

water. Apparently in this act the tissues of the head are exploded in order that the uterus may escape (Fig. 161).

When the tube has been extruded an inch or thereabouts, it suddenly fills with an opaque whitish material, ruptures, and collapses, the fluid spreading over the surface of the erosion. If a little of the fluid, either that which has welled up through the hole, or that which has escaped from the ruptured tube, be placed under the microscope, it is seen to contain myriads of dracunculus embryos lying coiled up, almost motionless, with their tails projecting in a very characteristic manner (Fig. 162). If now a drop of water be instilled below the cover-glass, the embryos may be observed to unroll themselves, and, in a very short time, to swim about, *more suo*, with great activity. If the douching be repeated after an hour or longer, a further supply of embryos can be obtained; and this can be continued from time to time until the worm has emptied herself. Apparently the cold applied to the skin of the host stimulates the worm to contract, and thereby force out her

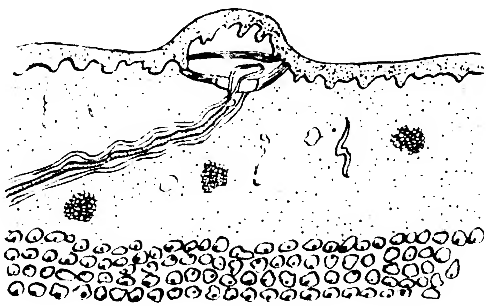


Fig. 161.—Diagram of vesicle caused by guinea-worm, showing prolapse of the uterus in the act of discharging embryos into the blister cavity.

(*After Fairley and Glen Liston.*)

uterus, inch by inch, until it is completely extruded. The repeated birth of a limited number of progeny each time the skin of the host comes into contact with water is therefore a wonderful provision of nature. Aberrant forms of embryos have been described by Moorthy and Sweet (p. 967).

The first symptoms appear usually simultaneously with the beginning of the blister-formation and consist of urticaria, nausea, vomiting, diarrhœa, asthma giddiness and fainting and it is believed that they are due to absorption of the toxin emitted by the worm to form the initial skin blister. The nature of the symptoms strongly suggest an anaphylactic reaction, and goats injected with guinea-worm extracts show similar symptoms, while injections of adrenalin bring about rapid improvement. Later symptoms result from the invasion of the ulcer by bacteria.

Should the worm become injured or lacerated while lying in the subcutaneous tissues, severe local reaction may develop. The part becomes extremely painful, inflamed, and œdematous, and cellulitis, due to secondary bacterial infection, may result, caused by the downward growth of staphylococci and streptococci from the skin. Arthritis, synovitis, epididymitis, contractions of tendons, and ankylosis of joints have even been known to

ensue. In some patients, generalized systematic symptoms accompany the premonitory urticaria, such as pyrexia, giddiness, dyspnœa, and vomiting; and gastro-intestinal symptoms have been noted during the early stages of guinea-worm infection, associated with an increase of eosinophile cells in the blood; this is due to the absorption of a specific toxin, and alarming symptoms may be produced in laboratory animals by intravenous injection of extracts of the adult dracunculus and the embryos.

That the cellulitis associated with guinea-worm is due to the excretion of toxins by the mature parasite has been shown by Fairley and Glen Liston, who failed to produce any local or general reaction by subcutaneous injection of the embryos themselves. Botreau-Roussel and Huard have described a

Fig. 162. Embryos of *D. medinensis*. (*Photomicro. Mr. H. B. Bristow.*)

specific non-bacterial arthritis, especially of the knee-joint, associated with the presence of a guinea-worm in the vicinity.

Lester from Dar-es-Salaam reports the discovery of an entire guinea-worm found coiled in a hernial sac; it was kept alive in the laboratory for twelve days after removal. According to Trewn, guinea-worms may present themselves after as long an interval as fifteen years from the time of infection. Massive infections are also reported, and this authority has seen as many as 56 adult worms in one person at the same time.

Diagnosis.—This is, as a rule, sufficiently obvious. In cryptic infections there is generally an eosinophilia. If the worms cannot be seen they can be felt underneath the skin. In those cases in which both these methods fail, screening with the X-rays has been found of use; the injection of 2 c.c. of 10-per-cent. collargol into the worm renders it opaque (Hudellet, 1919). Effete and calcified worms are easily demonstrated by skiagraphy. (Plate XXVII.)

An *intradermal test* for diagnostic purposes has been introduced by Ramsay. The antigen is obtained by adding to 100 c.c. of ether 0·25 grm. of dried powdered guinea-worm, with frequent shakings at room temperature for two hours to remove the lipoids. The dried, ether-free residue is extracted with shaking for four hours, in 100 c.c. of 0·85-per-cent. solution of sodium chloride at 37° C. Subsequent to centrifugation, it is passed through No. 6 Seitz filter, and 0·25 c.c. of this is used for injection. A positive wheal is 2–3 cm. in diameter, with outrunners.

Sequelæ of guinea-worm infection.—Subacute sterile abscesses are occasionally met with, due to premature death of the female *D. medinensis*, with the liberation of embryos into the subcutaneous tissue. The condition is diagnosed by the presence of a deeply situated fluctuating swelling, no communicating with the exterior. In synovitis and arthritis, the exudate may be serous or purulent. Generally there is an associated cellulitis, the synovial membrane being involved by direct spread through the adjacent tissues. Permanent deformities are invariably associated with sepsis and a history of prolonged illness in the recumbent position. Bony ankylosis is rare. The joints mainly involved are the knee and the ankle, while the tendo Achillis and ham-strings are not infrequently contracted. Calcified worms may be symptomless but they have been found entering the knee-joint. However, Connor (1922) has drawn attention to cases in which previously the diagnosis of chronic rheumatism, traumatic synovitis, periostitis, and sciatica have been made, where X-ray examination revealed calcified worms.

Treatment.—Formerly it was the custom, so soon as a guinea-worm showed herself, to attach the protruding part to a piece of wood and endeavour to wind her out by making a turn or two of this daily. Sometimes these attempts succeeded ; just as often the worm snapped under the strain. The consequences of this accident were often disastrous. Myriads of young escaped from the ruptured ends into the tissues, and violent inflammation and fever, followed by abscess and sloughing, ensued ; weeks, or months perhaps, elapsed before the unhappy victims of this rough surgery were able to get about. Too often serious contractions and ankylosis from loss of tissue and inflammation, and even death from septic trouble, resulted.

If a guinea-worm be protected from injury, and the part she occupies frequently douched with water, her uterus will be gradually and naturally forced out inch by inch and emptied of embryos. Until this process is completed she resists extraction ; possibly the hook at the end of her tail assists her to maintain her hold. When, in from fifteen to twenty days, parturition is completed, which can easily be ascertained by the douching experiment already described, the worm is absorbed or tends to emerge spontaneously. A little traction, if practised then, may aid extrusion. Traction, however, must not be employed so long as embryos are being emitted. When located by X-rays and collargol, the worm may be dissected out (Hudellet).

The parasite may be killed by injecting her, by means of a syringe, with solution of bichloride of mercury, 1 : 1000; after twenty-four hours, extraction is usually easily effected. If the worm has not shown herself externally, but can be felt coiled up under the skin, the coils should be injected, through several punctures, with a few drops of the same solution. Fairley and Glen Liston advocate aspiration of the blister-fluid previous to extraction, followed by precautions to avoid sepsis. The surface should first be painted with tincture of iodine. After a period of forty-eight hours, they advise actual excision of the worm if lying convoluted in a limited space; failing this, intermittent traction on the worm should be combined with massage. The subcutaneous injection of 9–10 min. of 1 : 1000 adrenalin hydrochloride immediately relieves the distressing prodromal symptoms from absorption of toxins such as urticaria and asthma.

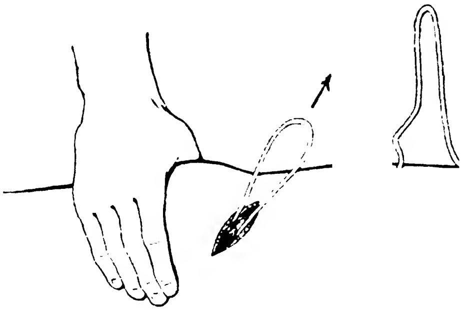


Fig. 163.—Diagram of removal of guinea-worm. (*After Fairley.*)

To complete extraction of the worm, the operative procedure is described in detail as follows: It is applicable whether a blister has formed or not, or whether a sinus is present. The skin overlying the worm at some distance from the guinea-worm ulcer is infiltrated with cocaine and adrenalin (2 c.c. of 1-per-cent. cocaine and 1 c.c. of 1 : 2000 adrenalin). An incision is made at right angles to the line of the worm through the anæsthetized tissues. The whitish fibrous sheath of the worm being exposed, the superior surface is incised longitudinally and a small strabismus hook is inserted inside its interior. By these means the female *D. medinensis* is hooked out. The loop of the worm is held lightly in the fingers while intermittent traction and massage are again employed. Should it be impossible to liberate the distal end of the parasite, a second incision is made over another palpable segment of the worm, and both ends of the central loop are now cut across and the intermediary portion removed. It is most important that the proximal head portion of the worm should be removed through the sinus, not drawn through the sheath in the subcutaneous tissues in the reverse direction, or otherwise there will be pollution with organisms from the mouth of the sinus (Fig. 163.)

Intravenous injections of tartar emetic appear to exert little or no influence upon the guinea-worm.

It is advantageous to mention a native treatment which is practised on the Gold Coast, and has achieved a local reputation. The part of the leg or arm presenting the guinea-worm is rubbed first with olive oil and subsequently with mercurial ointment, daily and vigorously for a week or longer. This is said to kill the underlying worm, which can then be easily extracted.

Prophylaxis.—From what has been stated with regard to the rôle of cyclops, it is evident that prevention is merely a question of protecting drinking-water from pollution by guinea-worm patients. Leiper has shown that, by raising by a few degrees the temperature of the water in which cyclops are living, these crustaceans are killed. He suggests heating by a portable steam generator the water in wells and water-holes known to be sources of guinea-worm infection. Alcock found that the addition of a trace of potash to the water is equally effective. In Mysore, Moorthy finds that step-wells are the greatest source of infection, especially in the high-caste Hindus. When barbel fish (*Barbus puckelli, B. ticto, Rasbora donicornicus*), which feed voraciously on cyclops and also on guinea-worm larvæ, are introduced, the guinea-worm disappears. Otherwise the wells must be treated every fourteen days with *perchloron* (bleaching-powder substitute).

CHAPTER XLIII

PARASITES OF THE LUNG AND LIVER

I. PARAGONIMIASIS (ENDEMIC HÆMOPTYSIS)

History.—This disease and the characteristic eggs appearing in the sputum of its subjects were described by Baelz and Manson in 1880. Ringer, in 1881, was the first to find the mature parasite, which was afterwards described by Cobbold under the name of *Distomum ringeri*; subsequently it was recognized to be closely related to the previously described *Paragonimus westermanii* of the tiger. The main features of its life-history and pathological bearings have been worked out since by Japanese observers. Closely allied species are found in the pig, dog, cat, otter, and ichneumon (*see* Appendix, p. 901).

Geographical distribution.—Paragonimiasis occurs in China, Japan, Korea, Formosa, and the Philippines. In many of the endemic districts a notable percentage of the population is affected. The parasite which gives rise to this peculiar form of blood-spitting has been found in the United States in the cat, in the dog, and in the domesticated hog, but, so far, no cases of the disease in man have been reported from America.

Ætiology.—The fluke, *Paragonimus ringeri* (*westermanii*), is reddish-brown in colour, thick and fleshy, oval in shape, and measures 8–20 mm. in length by 5–9 mm. in breadth. Development of the parasite proceeds in the fresh-water snail *Melania*, and thereafter the larva encysts in several species of fresh-water crabs and crayfish, especially the mitten crab (*Eriocheir*), a species which first found its way into Europe ten years ago. It is now almost universally distributed in the Elbe and the Weser in North Germany.

The young parasites hatch in the ileum and in 24–42 hours they penetrate the intestinal wall near the jejunum, reach the peritoneal cavity, and make their way to the diaphragm by penetrating the tendinous portion. Penetrating beneath the pleura the larvæ reach and pierce the parenchyma of the lungs, where cysts are formed. In other organs they do not reach perfect growth (*see* Appendix, p. 903). Man is infected by eating raw or improperly-cooked crabs, of which the Koreans are very fond, while the raw juice of crayfish is taken as a medicine for diarrhœa and also for whooping cough.

Pathology.—The lungs do not at first present any unusual appearances but, on looking closely, small brown spots are thickly distributed over the entire surface of the pleura and many tumour-like swellings of a deep red colour, in which the parasites are situated, can be seen. On making a section of the lungs in this disease, a larger

or smaller number of what are known as " burrows " are discovered scattered about the organ, particularly towards the periphery. These burrows consist of areas, somewhat larger than a filbert, of infiltrated lung tissue in which can be seen a number of tunnels filled with the same material that constitutes the characteristic sputum, and also containing one, two, or more small trematodes. The septa between the tunnels may break down and a considerable cavity be thus produced ; and as this occurs in connection with one of the bronchi, with which the tunnels always communicate, it may give rise to the appearance of a dilated bronchus. One burrow may communicate with another. It is estimated that the number of eggs coughed up in twenty-four hours is over 13,000. Tubercle-bacilli and paragonimus eggs are frequently found together.

When first discovered, it was supposed that *P. ringeri* was confined to the lungs. We now know that it may affect the liver, peritoneum, testes, intestine, skin, muscle, and brain. In the brain it forms a sort of tunnelled tumour similar to those in the lungs.

Musgrave, in his study of the pathology, points out that the peculiar bluish, cyst-like burrows of the parasite occur in many organs and tissues. The infiltration of the tissues by the eggs produces, especially in the serous membranes, little brownish-red patches sometimes visible to the naked eye. The intestinal mucosa is a common seat of infiltration, which gives rise to inflammatory reaction, ending in ulceration and the appearance of eggs in the fæces. The eggs may find their way into the spinal cord, as reported by Robertson, and produce in life a transverse myelitis. No fewer than 100 mature parasites have been found in a psoas abscess.

Symptoms.—The symptoms generally begin so insidiously that it is impossible to fix their onset with accuracy. The subjects of endemic hæmoptysis have a chronic cough, and a vague feeling of distress in the chest, which is usually most urgent in the morning on rising. The fits of coughing eventuate in the expulsion of a peculiar rusty-brown, pneumonic-like sputum. This sputum can be produced at will almost at any time, and often in considerable quantity. In addition to the chronic cough and the tenacious rusty expectoration referred to, the patient is liable to irregular attacks of hæmoptysis. Though usually induced by violent exertion, occasionally such attacks come on without apparent cause. The hæmoptysis may be trifling ; on the other hand, it may be so profuse as to threaten life—at all events, to cause intense anæmia. Ogi states that an outstanding physical sign in chronic cases is clubbed fingers. The physical examination of the chest is mainly negative. The patient is well-nourished. Resonance is usually normal with a tendency to hyper-resonance, while râles can be demonstrated only in a few instances.

The sputum.—On placing a minute portion of the viscid, pneumonic-like sputum under the microscope, its peculiar colour is found to be due partly to red blood-corpuscles, partly to a crowd of dark-brown,

thick-shelled, operculated eggs (Fig. 164). Besides pus-corpuscles there are seen large numbers of eosinophile cells. Charcot-Leyden crystals are often present. The eggs vary a good deal in size and shape; they are all distinctly oval, have a yellow, smooth, double-outlined shell, and measure from 80 to 100 μ in length by 40 to 60 μ in breadth. If the sputum be shaken up in water, and the water be renewed from time to time, in the course of a month or six weeks—longer or shorter according to temperature—a ciliated miracidium is developed in each egg. When the egg is mature, on placing it on a slide and exercising slight pressure on the cover-glass, the operculum will be forced back, and the miracidium will immediately emerge and begin to swim about and gyrate in the water.

Abdominal symptoms in some cases may also be present; they consist of dull abdominal pains and occasional diarrhœa. The abdominal wall feels hard to the touch and is tender; at the same time symptoms of liver cirrhosis, appendicitis, enlargement of the prostate, epididymitis, and adenitis may be present.

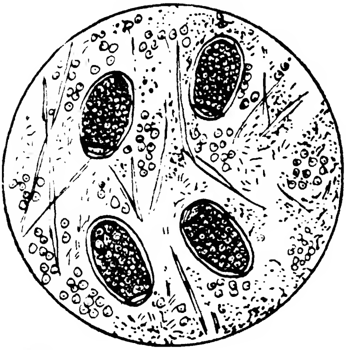


Fig. 164.—Eggs of *Paragonimus ringeri* in sputum.

Cerebral.—When the disease affects the brain, especially in children, a peculiar form of Jacksonian epilepsy may be a feature for a considerable period, and may eventuate in hemiplegia, aphasia, visual disturbances, pareses or monoplegias of various degrees.

Generalized.—In what is known as generalized paragonimiasis, in addition to the symptoms noted above, generalized lymphadenitis, especially affecting the axillary and inguinal groups, is present, associated with cutaneous ulcerations.

Diagnosis.—Diagnosis of endemic hæmoptysis is at once established by the discovery of the characteristic eggs in the almost equally characteristic sputum. The sputum is sticky, not foamy, and resembles that of pneumonia. Charcot-Leyden crystals are usually present. Râles and other physical signs of lung consolidation are not usually discoverable. If the intestine or liver is implicated, eggs may appear in the stools.

In the case of one-sided convulsions, or in hemiplegic affections occurring in a native of, or in a visitor from, the countries in which this trematode is endemic, the sputum should be examined on the chance of discovering evidence of the parasite. Should eggs be found, there is a strong presumption that the cerebral trouble arises from a trematode tumour in the brain.

In the endemic zones of paragonimiasis, even in the absence of

eggs in the sputum, Musgrave recommended that this parasite should be suspected in cases of chronic epididymitis, enlargement of the lymph-glands or prostate, liver cirrhosis, and skin ulceration. As some of these conditions are also found in *Bilharzia japonica* infection, one should be careful to distinguish the operculated eggs of paragonimus from those of the other parasite. It is desirable that the sputum be examined bacteriologically to exclude the tubercle bacillus. Blood examination usually discloses a moderate leucocytosis of about 15,000 and, curiously, there is not usually any rise in the eosinophile cells.

The cutaneous ulcerations have to be distinguished from those of oriental sore.

Bercovitz reports that X-ray examinations of the lungs are very disappointing, while *lipiodol* infiltration shows no cavities, probably because paragonimus infection is situated at the periphery of the lung. Wang and Hsieh, on the other hand, have described well-defined opacities and isolated infiltrations situated in various parts of the lung field.

Ando has described a Bordet-Gengou test, using an extract of the body of the adult worm as antigen. This probably, when fully worked out, will constitute an efficient aid to diagnosis in obscure cases. From the clinical aspect paragonimiasis has to be distinguished from bronchiectasis more than any other condition.

Treatment.—Hitherto no means of expelling the parasite from the lungs has been discovered. In the case of cerebral paragonimiasis, it might be possible by an operation to remove the parasite and associated tumour, and thus afford a chance of recovery in what has hitherto proved a fatal condition. Kobayashi and Ando have reported encouraging results with emetine, which is said to lessen the sexual activity of the trematodes. The drug is injected intramuscularly in doses of 1·25 c.c. of a 2-per-cent. solution four times daily for five days, but it must be used with great caution, especially in cases where there is any myocardial trouble. This has been confirmed by Bercovitz, who gives emetine in 1-gr. daily doses for periods of seven days. To and Ko have given carpain by subcutaneous 5-per-cent. injections in normal saline. The total quantities were 0·3 grm. over six days, 1·1 grm. over 23 days. Bercovitz also reports that marked improvement follows lipiodol injections into the bronchi.

Prophylaxis in this, as in so many other animal-parasite diseases, lies principally in the direction of securing a pure water supply for drinking and bathing purposes, and avoiding all uncooked articles of diet, especially crabs and crayfish, which might be supposed to contain the young parasites. The sputum should be destroyed. In Chosen, Korea, an enlightened Government has waged a campaign against crabs, and has rendered their sale unlawful, while the populace is being educated about the dangers by means of posters and advertisements.

II. CLONORCHIASIS

Geographical distribution.—The trematode responsible for this disease has been found in many Eastern countries including India, Mauritius, Japan, Korea, Formosa, China, and Tonquin. In South China, Faust and Khaw have determined that the fish-raising industry is responsible for the high incidence in Kwantung Province. In Central Japan, according to Katsurada, there are certain districts in which it affects from 56 to 67 per cent. of the population, and Léger records finding the eggs in 50 per cent. of the natives of the East Coast of Indo-China. Recently an endemic area has been discovered on the Pacific Coast of California, the infection having been imported by Chinese immigrants.

Ætiology.—The parasite, *Clonorchis sinensis*, measures 10 to 20 mm. in length by 2 to 5 mm. in breadth; it is oblong, narrow, flat, and somewhat pointed anteriorly, reddish in colour, and nearly transparent. Development outside the human body takes place in two different intermediary hosts—primary, a mollusc, *Bithynia*; and secondary, several species of freshwater fish of the carp family. For further details, *see* Appendix, p. 896.

Pathology.—*C. sinensis* inhabits the bile-ducts. It thickens the walls of the biliary canals and expands them in places into cavities and diverticula as large as filberts, the walls of which are thickened with fibrous tissue. In these cavities vast numbers of parasites may be found. The diverticula communicate with the bile-ducts, along which the eggs of the parasites, and sometimes the parasites themselves, escape into the intestine. The affected liver is enlarged as a whole, although the tissue in the immediate neighbourhood of the diseased bile-ducts is atrophied. The spleen, also, may be hypertrophied and the intestine in a condition of chronic catarrh. Some instances are recorded of the presence of this trematode in the pancreatic ducts, in the duodenum, and in the stomach, associated with ascites, and even with anasarca. According to Hoeppli it may produce carcinomatous changes, while Kown and his associates have found growths in the liver, apparently connected with clonorchis infection.

This parasite, which for long was supposed to be practically innocuous, is now held to be the cause of a serious cirrhosis of the liver, which may terminate fatally; indeed, there can be no doubt of this when one considers that in some of the cases recorded several thousand parasites were present. Sambuc and Baujean counted 21,000 at one autopsy, and reckoned the total weight of the parasites at 300 grm.

Symptoms.—When the infection is severe the liver becomes enlarged, and chronic diarrhœa, with recurring attacks of jaundice, sets in. Late anasarca appears, and gradually a cachexia, resembling that of sheep-rot, is established, which, in the course of several years, may prove fatal. In lighter infections there is indigestion, epigastric distress and, curiously, night-blindness (Bercovitz). The Editor has seen one case in which clonorchis appeared to be the cause of acute cholecystitis (strawberry gall-bladder).

Radiograph of leg showing guinea-worm injected with lipiodol.
(*Dr. Botreau-Roussel.*)

GUINEA-WORM.

PLATE XXVII

RADIOGRAPH OF CALCIFIED CYSTICERCI IN THE THIGH.

(*Major-General W. P. MacArthur, Trans. Roy. Soc. Trop. Med. and Hyg.*, 1934.)

PLATE XXVIII

Diagnosis.—It would be well to bear in mind this and other parasites in approaching the diagnosis of obscure hepatic disease associated with diarrhœa and jaundice in patients from the East. The discovery of the eggs (Fig. 165) in the stools should guide to a correct diagnosis. Associated with this disease there is generally a considerably leucocytosis of over 30,000 and an eosinophilia of over 40 per cent. Toullec and Riou recommend the duodenal sound as a ready method of diagnosis, because in the aspirated bile large numbers of eggs may be demonstrated, even when they are not present in the stools.

Treatment.—So far, no specific treatment has been found. The

Fig. 165.—Eggs of *Clonorchis sinensis* in fæces. × 250. (*Photomicro: Dr. John Bell.*)

patient should be removed to a non-infected area and given nourishing food. Recently, salol has been reported as beneficial in the analogous liver-fluke disease of sheep. Neither emetine injections nor tartar-emetic treatment are of any avail.

Faust has found that in experimental cats, gentian-violet administration *per os*, after preliminary stimulation of ovulation, causes death of the fluke for which this dye appears to have a special affinity. About 80 mg. per kilo weight was found to be the correct dosage. Unfortunately this drug appears to be toxic to the host, but it opens up an important line of clinical research.

Continuous non-surgical bile drainage has been extensively practised in Korea by means of the duodenal tube. It is found necessary to cocainize the throat to prevent reflex vomiting. As a rule, it is possible to allow the tube to remain in position continuously for several days

and observe the flow of bile. During the day the bile is collected every two hours, following stimulation by 50-per-cent. magnesium sulphate through the tube. The extracted bile is then examined microscopically for clonorchis eggs, and the number per 4 cu.mm. is counted. It is, however, necessary to state that this procedure does not get rid of all the clonorchis eggs, but it is useful in getting rid of toxic material, and the results are most spectacular in cases when the liver is enlarged and tense. Biliary drainage is not always a harmless procedure, and is sometimes followed by shock.

Prophylaxis.—Manifestly, the Chinese habit of eating raw fish is to be deprecated. Animals and men harbouring the parasite should be prevented from fouling water, whether used for drinking or bathing, or for agricultural purposes.

CHAPTER XLIV

INTESTINAL PARASITES

I. ASCARIASIS

Definition.—Infection of the alimentary tract with the roundworm, *Ascaris lumbricoides*. This worm is of large size and familiar appearance; it may give rise to no special symptoms save inconvenience; but on occasions may be the starting-point of complications of considerable severity. The worm itself and its life-history are described on p. 929.

Symptoms.—The normal situation of ascaris in the bowel is the jejunum. There, as can be shown by skiagraphy, the worms lie motionless, curled up in bundles, so that the bowel can be stuffed with worms like a well-filled sausage.[1] The toxic symptoms produced by ascaris infection are probably attributable to *ascaron*, a mixture of albumoses and peptones. Fülleborn and Kikuth have studied the allergic phenomena of ascaris infection. Certain anaphylactic symptoms are well known. Some individuals manifest a peculiar sensibility to ascaris emanations, and even entering a laboratory where ascaris worms are being dissected, is enough to cause conjunctivitis, urticaria, asthma, and even "fever." The skin of these people is extraordinarily sensitive to minimal doses of ascaris substance, and in a few minutes a red and extremely sensitive wheal is produced. The passage of a worm is attended by an intolerable itching of the anus and the vomiting of the same may occasion œdema of the glottis. In children, ascaris infection produces pallor of the face with blue rings under the eyes and sometimes interference with nutrition; on the other hand, the infection may never be suspected until the eggs are found in the stools. Some clinicians attach some significance in diagnosis to Couillard's sign, *i.e.*, the prominence and redness of the fungiform papillæ on the tip and sides of the tongue.

In many instances the ascaris gives rise to no very noticeable symptom; in others it is to be credited with a number of ill-defined gastric and perhaps nervous troubles—capricious appetite, foul breath, restless sleep, peevishness, vague abdominal pains, nausea, and so forth. It may cause urticaria of a most pronounced type. Sometimes the worms get into the stomach and are vomited, their appearance giving rise to no inconsiderable alarm. They may even creep

[1] The worms ingest the barium, and their situation is clearly shown in X-rays by the opaque outline of the intestinal tracts.

up the œsophagus and into the mouth, or out by the nostrils. Cases are on record in which they caused suffocation by wandering into the rima glottidis. When aggregated into masses in the intestines they may cause a volvulus, and even intestinal obstruction. They have been known to enter the pancreatic and the bile-ducts and give rise to jaundice and abscess of the liver; to cause acute hæmorrhagic pancreatitis by blockage of the bile-duct; to penetrate the intestinal wall and escape into the peritoneum, causing peritonitis; or to burrow into the abdominal walls and cause abscess. Ascaris eggs have been demonstrated in pearl-like nodules encysted in the peritoneum and mesentery. They may invade the lumen of the appendix and cause appendicitis, and their eggs may occur in profusion in this situation. In women, they may invade the generative tract, and have been found encysted in the Fallopian tubes.

Although "ascaris pneumonia" is not often diagnosed in man, its presence has been suspected in West Indian negroes. In experimental animals heavily infected with ascaris larvæ death takes place from pneumonia after four to five days. The larvæ, in their wanderings through the lung capillaries, must give rise to considerable disturbances. In North America pneumonia is much feared by some breeders, as the ascaris of the pig is very similar to, and has the same life-history as, *Ascaris lumbricoides*. The ascaris of the pig is a definite biological species, as it cannot develop to maturity in man, nor can the reverse take place.

The experiment of Koino, a Japanese investigator, must be mentioned. He swallowed 2,000 ripe human ascaris eggs. Six days later he was attacked by a definite pneumonia with dyspnœa, cyanosis, a pyrexia of 104° F. and a fever which lasted seven days. The sputum was profuse from the eleventh to sixteenth days, and contained ascaris larvæ of which 202 were counted. The liver was enlarged and there was congestion of the conjunctiva, and there were severe muscular spasms. After a period of fifty days from the time of infection, 667 ascaris, varying in length from 3–8 cm., were voided. It is said that during their migrations in the lung the larval worms may give rise to hæmoptysis.

It is estimated that each female ascaris in the bowel produces 2,000 eggs for every gramme of fæces.

Diagnosis.—It is well, when puzzled over some obscure dyspeptic condition in tropical patients, to bear the ascaris in mind. If, for some reason, it is undesirable to give santonin or oil of chenopodium diagnostically, the stools ought first to be examined with the microscope. Various concentration methods may be employed for demonstrating the eggs (*see* p. 1031). If they are found, a dose or two of santonin may clear up the diagnosis and cure the patient; if no eggs are found, the drug may be withheld and the idea of ascarides abandoned.

Ascaris infection is usually associated with an eosinophilia, but this is by no means so reliable as was formerly considered, and the Editor has seen heavy infections with this parasite without any increase of

the eosinophile cells at all. During the invasion stage, when the larvæ are resident in the lungs, there is a very definite eosinophilia, but this diminishes as the worms enter the intestinal canal. In America, Jeller, Kaspari, and Leathes found in European children an average eosinophilia of 9·9 per cent. and in negro children about 5·3 per cent.

The cutaneous reactions to *Ascaris antigens* are of little practical importance and Fülleborn considers the "scratch test" with powdered ascaris more reliable than the intradermal injection. In many infected individuals the test remains negative, and moreover, a person who has once been infected and cured, remains in a sensitive condition for the rest of his life.

Treatment

The most widely emphasized drug for the treatment of ascaris infection is **santonin**, but it is by no means as effective as was formerly thought, and is apparently more lethal to the female than to the male worms, while it has been proved that after several treatments many individual worms escape. It is apparently effective to a limited extent when given in the form of suppositories. The dose by the mouth is ½–1 gr. (0·032 to 0·065 grm.) for a child, and 3–5 gr. (0·194 to 0·324 grm.) for an adult. A good method of giving the drug is to prescribe three doses on successive nights, the first and the last dose to be followed by castor oil the next morning.

Santonin, $C_{12}H_{18}O_3$, is a crystalline lactone obtained from santonica, which consists of the dried unexpanded capitula of *Artemesia cina*, Berg. (Fam. *Compositæ*), a small undershrub which grows plentifully in Turkestan and is known as "Levant wormseed." It is almost insoluble in water, but soluble in 90-per-cent. alcohol (1 : 44), chloroform (1 : 2·5) and castor oil (1 : 200). When exposed to sunlight it turns yellow. It does not kill the worm, but probably affects its vitality, causing it to migrate to the lower bowel. The dose is best prescribed with sugar and 3·5 gr. of calomel. It is more active in a mixture with castor oil such as:

℞	Santonin	gr.iv (0·259 grm.)
	Ol. ricin.	ʒiii (10·65 c.c.)
	Mucil. acac.	ʒiv (14·21 c.c.)
	Syrup. simp.	ʒi (3·55 c.c.)
	Aq. menth. pip.	℥iss (42·63 c.c.)

This is taken after fasting in the morning, but is liable to cause symptoms of santonin poisoning.

The symptoms of santonin intoxication are a green or yellow urine, if acid, purplish or red, if alkaline. It causes yellow vision, headache, vertigo, nausea, and even epileptiform convulsions, and it may produce irritation of the kidneys, with painful micturition and hæmaturia.

An alternative method consists of taking santonin, gr. 5, with calomel, gr. 2–3, on three successive nights followed by a saline purge, ℥ss of magnesium sulphate, six hours afterwards.

Oil of chenopodium (*see* p. 815) is sometimes more effective than santonin. It may be given in a mixture with liquid paraffin (one ounce) or in capsules. The maximum dose is 24 minims (1·421 c.c.), and is usually given in two portions of 12 minims each within a quarter of an hour of each other. Capsules of oil of chenopodium contain three minims each of the drug. Eight of these should be given early in the morning in two portions of four capsules each. It has the added advantage, which it shares with carbon tetrachloride, of being efficacious for the ancylostome and tapeworm as well.

Carbon tetrachloride (tetraform) is given in the same manner as for ancylostomiasis, with the same precautions (*see* p. 815). It is given alone, in capsules, in syrup, or with liquid paraffin in doses of one drachm for an adult and proportionately less for children. It should be followed by a dose of salts such as mag. sulph., half an ounce.

The combined treatment of oil of chenopodium together with carbon tetrachloride is the most efficacious in the Editor's opinion. They may be given together in a mixture as in ancylostomiasis, but it is probably best to give the carbon tetrachloride on one day, and the oil of chenopodium on the following. The worms, when expelled, are always dead and sometimes disintegrated. It is important to warn the patient that they may not appear in the dejecta for two, or even three days, after the completion of the treatment. Fatalities from carbon tetrachloride treatment have been reported. In the case of ascaris they may be due to blockage of the bowel, or of the bile-ducts, by masses of dead worms.

Hexylresorcinol.—In America this drug has recently come into favour as a vermifuge, for ascaris. Crystals in gelatin capsules or sugar-coated pills are given by the mouth in doses varying from 0·1 to 1 grm. three times daily, according to the age of the patient (0·1 grm. for each year up to ten). The drug should be given on an empty stomach and should be followed by a saline purge.

II. ANCYLOSTOMIASIS[1]

Synonyms.—Uncinariasis; Hookworm Disease; Egyptian Chlorosis.

Definition.—A disease in its more pronounced forms characterized by great anæmia, debility, and cardiac incompetence, due to the absorption of the toxins of *Ancylostoma duodenale* and *Necator americanus,* nematodes which inhabit the small intestine, and may be sometimes present in enormous numbers. The ancylostome, in many tropical countries, on account of the dangerous cachexia—ancylostomiasis—to which it gives rise, amounts to a positive curse.

[1] **A complete bibliography on this disease has been published in a volume by the Rockefeller Foundation International Health Board. Publication No. 11.**

History.—The worm, now known as *Ancylostoma duodenale*, was first recognized by Dubini in 1838, and in 1843 he published a detailed account of it, but apparently did not recognize its pathogenic importance. Bilharz (1853) and Griesinger (1854) connected the parasite with the extremely severe chlorosis prevalent in Egypt, but it was not until the very fatal epidemic of anæmia among the miners in the St. Gothard Tunnel (in 1880) had called the attention of European observers to the subject that the importance of this parasite as a pathogenic agent began to be properly apprehended.

Geographical distribution.—The ancylostome has been found so widely diffused that it may be said to occur in all tropical and subtropical countries. It occurs in Belgium, and was found by Haldane to be the cause of an epidemic of severe anæmia in a Cornish mine. In northern countries it is rare; but it is abundantly present in the south of Europe, and in the tropical and subtropical regions of Asia and America. It is especially prevalent in Siam, in South China, and Malaya. In India, Ceylon, and the East Indies it is a source of grave disability in plantations, mines, etc. It occurs abundantly on most of the Pacific islands, and exists in North and South Queensland and in Egypt.

Ætiology (Fig. 166).—The normal habitat of *A. duodenale* is the small intestine of man, and particularly the jejunum; less so the duodenum, rarely the ileum or lower reaches of the alimentary canal; very occasionally it is found in the stomach. In these situations it attaches itself by means of its powerful buccal armature to the mucous membrane, from the blood of which it obtains a plentiful supply of nourishment. It is supposed to shift its hold from time to time, the abandoned bite continuing to ooze blood for a short period. It is said to be very prodigal of the blood it imbibes, the red corpuscles passing through its alimentary canal unchanged, and the plasma alone being utilized.

Fig. 166.—Ancylostoma duodenale. Nat. size. (*Dubini.*)
a, Male; *b*, female.

The male and female ancylostomes — present generally in the proportion of one of the former to three of the latter—do not differ so much in size as is the case with many of the other nematodes. The male (Fig. 166, *a*) measures 8–11 mm. in length by 0·4–0·5 mm. in breadth; the female (Fig. 166, *b*) 10–13 mm. in length by 0·6 mm. in breadth.

Necator americanus closely resembles *A. duodenale*, but is shorter and more slender (*see* Appendix, p. 934). At first it was thought to be confined to the American continent, but it has been found by Looss and others in pygmies from Central Africa, and by others again in Rhodesia, India, Ceylon, Fiji, the Philippines, and elsewhere. Near Darjeeling in India it is found as a pure infection (Lane), whilst in Egypt *A. duodenale* occurs alone.

Reproduction and mode of infection.—The female ancylostomes produce a prodigious and never-ending stream of eggs, which pass out in the fæces. In the body of the host the development of the embryo does not advance very far; but on leaving the human host it proceeds, in suitable circumstances, so rapidly in the egg that in one or two days a rhabditiform embryo is born. This minute

organism is very active, voraciously devouring what organic matter it can find and, for a week, grows rapidly and moults twice. After the second moulting it passes into a torpid condition, in which it ceases to eat, and growth is suspended. In this state is may live for weeks or months, moving about more or less languidly in muddy water, in mud, or in damp earth, but it is rapidly killed by drying. It is said that it may also encyst on blades of grass. Cort and others have shown that the larvæ lose their sheaths while living in the soil, and continue to exist in the unsheathed state. Arrived in its final host, after moulting again at the end of five weeks, it acquires sexual characters and the permanent adult form.

Looss has shown that the parasites reach the intestinal canal by a definite route, by boring their way through the skin. From the subcutaneous tissue they enter the blood-vessels and lymphatics, and by this channel are passively transferred to the lungs. *Here they leave the capillaries, enter the air-vesicles, and thence along the bronchi and trachea pass into the œsophagus, and so to the stomach.* It has been conjectured that during this passage the larva acquires the power of resisting the action of the gastric juice.

The duration of the life of *A. duodenale* in the intestine has not been determined ; some state it in months, others in years (Sonsino)—one to three. On account of liability to reinfection, this point—an important one as affecting prognosis—is difficult to determine.

The exact number of ancylostomes necessary to produce symptoms of disease has exercised much attention. Some consider that 100 worms are necessary to produce pathogenic effects and that 500 to 1,000 worms must be present for at least six months to produce well-marked hookworm disease. Others believe that very few ancylostomes, such as ten or so, may affect the general health and working powers.

According to Lane, the egg-laying capacity of a single female ancylostome is about 30 eggs per c.c. content of fæces per diem. Sweet, as the result of his studies in Ceylon, concludes that the average Cingalese has an intensity rate of hookworm infection of 2,200 eggs per grm. " basis-formed fæces," or as representing approximately one hundred ancylostomes. It is estimated that 53 per cent. of people have what is classified as " hookworm disease," the remainder being merely " carriers of worms."

In four persons from whom the worms were recovered, the average egg-output per day for each female worm was 28,080. Relatively it appears that the egg-count falls as the worm-count rises.

Pathology.—The exact rôle of the ancylostome worm in the production of anæmia is by no means as yet settled. The following theories have been put forward of the causation of anæmia :

(*a*) Chronic loss of blood.
(*b*) Anæmia due to absorption of specific toxin.
(*c*) External conditions such as diet and general hygiene.
(*d*) The damaged gut may play a rôle through repeatedly renewed bacterial infection.

On the whole the evidence points to the dietetic factor as playing the greatest part in undermining the resistance on the part of the host (de Langen). As already mentioned, the bodies of the victims of ancylostomiasis are not wasted ; on the contrary, there is plenty of fat in the usual situations. The appearance of plumpness is further increased by a greater or lesser amount of general œdema. There may be effusions in one or more of the serous cavities. All the organs are anæmic. The heart is dilated and flabby, its muscular tissue being in a state of pronounced fatty degeneration. The liver also is fatty, and so are the kidneys.

If the post-mortem examination be made within an hour or two of death, the ancylostomes, in numbers ranging from a few dozens up to many hundreds, will be found still attached by their mouths to the mucous surfaces of the lower part of the duodenum, of the jejunum, and perhaps of the upper part of the ileum ; but if the examination has been delayed for some hours the parasites will have loosed their hold, and are then to be found lying in the mucus coating the inner surface of the bowel. Many small extravasations of blood—some fresh, others of long standing—are seen in the mucous membrane, a minute wound in the centre of each extravasation representing the point at which a parasite had been attached. Sometimes blood-filled cavities, as large as filberts, are found in the mucosa ; each cavity enclosing one or two worms and, probably, communicating by means of a small hole with the interior of the intestine. Old extravasations are indicated by punctiform pigmentation. There may be evidence, in the shape of vesiculations and thickening of the mucosa, of a greater or lesser degree of catarrh. Occasionally, streaks or large clots of blood are found in the lumen of the bowel.

Recent researches on the blood by Fikri and Ghalioungui have shown that in ancylostomiasis, the average total blood-volume is 79·5 c.c. per kg. body-weight ; the average plasma volume in ancylostome anæmia is 62·6 per kg., so that the diminution of the total blood-volume can be accounted for entirely by the diminution of the red blood-corpuscles. The blood-picture is that of a secondary microcytic anæmia.

Microscopical examination of the liver and kidneys shows the presence, within the cells of the parenchyma, of grains of yellow pigment having the reactions of hæmatoidin—indicating an intravascular blood destruction such as occurs in pernicious anæmia and other diseases of which excessive hæmolysis is a feature. On this account, and also because he found granules of a ferrous nature in the liver-cells, Daniels concluded that the anæmia in ancylostomiasis is, in a measure, the result of blood destruction within the vessels by some toxic substance produced by the parasite and absorbed from the bowel. These results have not been confirmed by all other observers.

Symptoms.—It is not in every instance in which the ancylostome is present that consequences so serious ensue. There may be dozens of ancylostomes in the intestine without any appreciable anæmia, or, indeed, symptoms of any description whatsoever. Grave symptoms are the exception. One must be careful, therefore, to avoid concluding that the ancylostome is the cause of every pathological condition with which it may chance to concur.

On the other hand, many inhabitants of tropical and subtropical countries are in a state of chronic starvation. Living on coarse, bulky, innutritious food, they are prone to dilatation of the stomach

and dyspeptic troubles. In such, any additional cause of malnutrition, as a swarm of ancylostomes, and a daily though perhaps small loss of blood, may be sufficient to turn the scale against them. In those countries, as elsewhere, there are many who live just on the borderland between health and disease; to such the ancylostome may prove "the last straw that breaks the camel's back."

It may be that in some persons with special susceptibility a toxin developed by the parasite produces a special type of anæmia, as in certain cases of *Diphyllobothrium latum* infection.

According to Darling, a given number of *A. duodenale* produces a greater degree of anæmia than an equal number of *N. americanus*. It is estimated that twelve worms are required to cause a loss of 1 per cent. of hæmoglobin.

It is evident that as a complication of typhoid, of kidney disease, of dysentery, of malaria, in fact of any chronic or exhausting disease, the importance of this anæmia-producing parasite cannot be ignored.

The practitioner in the tropics, therefore, must be constantly on the look-out, in all cases of anæmia, of dyspepsia, and of debilitated conditions generally, for the ancylostome. He must bear in mind that this parasite, as will be presently pointed out, if permitted to remain in the intestine for a length of time, may be the cause not only of remediable anæmia, but of irremediable anæmia-produced degenerations of various organs. On this account, also, its early recognition becomes a matter of the first importance. It has been pointed out by many observers that ancylostomiasis is the source of considerable surgical risk, not only in that it renders the operative procedure more difficult, but also in that it retards convalescence. It is also said to increase the risk of delayed anæsthetic poisoning. Whenever possible, anthelminthic treatment should be instituted prior to operation, especially when a laparotomy is contemplated.

Further, ancylostomiasis is an important disease from the standpoint of the employer of native labour. The invaliding and inefficiency which it causes among coolies, not to mention the deaths, are often financially a serious matter to the planter and the mineowner. To them any wisely directed expense or trouble undertaken for the treatment and control of this helminthiasis will be abundantly repaid by the increased efficiency of the labourer.

The essential symptoms of ancylostomiasis are those of a progressive anæmia—an anæmia which is generally associated with dyspeptic trouble, but which, in uncomplicated cases, is not associated with wasting. If the progress of a case be unchecked, serous effusions and fatty degeneration of the heart ensue, and death may occur from syncope or from intercurrent complication.

One of the earliest symptoms of an extensive ancylostome invasion is pain or uneasiness in the epigastrium. This is generally increased by pressure, but for the time may be relieved by food. In some people it may produce an acute and ever-present epigastric pain, which closely

resembles duodenal ulcer and may often, in the Editor's experience, be mistaken for it. The appetite, sometimes defective, is more often ravenous, though its gratification is apt to give rise to dyspeptic trouble of various kinds—to colic, to borborygmus, and perhaps to diarrhœa of imperfectly digested food. Constipation may be present in some instances; irregularity of the bowels in others. The taste may be perverted, some patients exhibiting and persistently gratifying an unnatural craving for such things as earth, mud, or lime—what is called *pica* or *geophagy*. The stools sometimes, though rarely, have a reddish-brown tinge from admixture of half-digested blood. Sometimes they may contain small flakes of blood-tinged mucus. Pure blood is seldom passed: and an extensive hæmorrhage, unless there be concurrent colitis, is rare, although, post mortem, considerable quantities may be found in the small intestine. Fever of an irregular intermitting, or even a subcontinued type is common. On the other hand, the temperature may be constantly subnormal, or these conditions may alternate. After a longer or shorter time, symptoms of profound anæmia gradually disclose themselves. The mucous surfaces and the skin become pallid, the face is puffy, and the feet and ankles are swollen. All the subjective symptoms of a definite anæmia now become more and more apparent: there are lassitude, breathlessness, palpitations, tinnitus, vertigo, dimness of sight, mental apathy and depression, liability to syncope, etc. The circulation is irritable, and hæmic bruits can be heard over the heart and larger blood-vessels. Ophthalmoscopic examination may reveal retinal hæmorrhages.

From some of these symptoms, were it not that with the advancing anæmia there is no loss of weight, one might be led to suspect the possibility of tuberculous or cancerous disease, or of Bright's disease. So far from losing weight, the patient may appear quite plump; and though hæmocytometric estimates testify to a slow and steady fall in the corpuscular richness of the blood until the lowest limit compatible with life is reached, there is no true poikilocytosis as in idiopathic pernicious anæmia, no excessive leucocytosis as in leucocythæmia, and not necessarily any enlargement of lymphatic glands, liver, or spleen. There is generally a marked eosinophilia of about 7–14 per cent., though in rapidly fatal cases these cells tend to disappear. The depression in the hæmoglobin value of the corpuscles is considerably greater than the fall in their number.

The rate of progress is very different in different cases. In some a high degree of anæmia may be attained, and even a fatal issue, within a few weeks or months of the appearance of the first symptoms. Such rapid cases are rare; more frequently the disease is exceedingly chronic, ebbing and flowing, or slowly progressing, through a long series of years. Acute cases develop terminal diarrhœa with passage of much mucus and, occasionally, blood. These cases are apt to be mistaken for various forms of dysentery.

Should such serious ancylostomiasis occur before puberty, the growth and development are apt to be delayed and stunted (Fig. 167).

There appears to be some reason for the belief that after generations of exposure to this infection a certain degree of tolerance is attained.

It is not surprising that the severe nutritional changes associated with ancylostomiasis affect the mental powers of an afflicted population. Prolonged exposure in the European has led to the production of a race known as the "mean white," stunted both in mental and in physical capacity. In Jamaica, in districts where the whole population suffers from ancylostomiasis, not only are the people intensely indolent, but are also predisposed, on this account it is said, to larceny and other crimes.

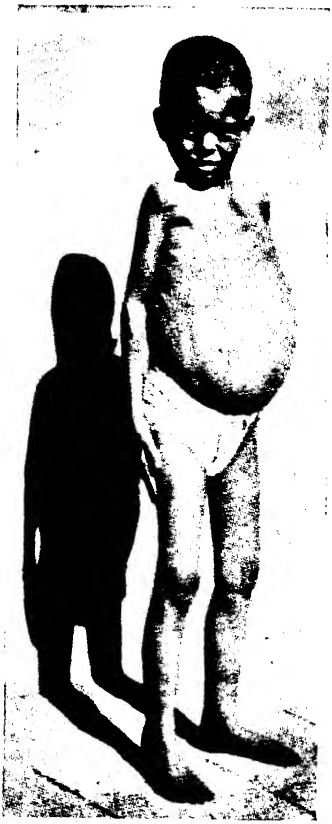


Fig. 167.—Ancylostomiasis in a South American Indian boy, showing stunted growth, characteristic facies, and protuberant abdomen. (*By permission of the Rockefeller Foundation.*)

The practitioner in the tropics should always be on the look-out for subacute infections in Europeans on plantations and in mines. This does not apply solely to the men, but to their wives as well. The Editor has found that, in his experience, minor degrees of anæmia, an undue tendency to fatigue, lassitude and digestive disturbances are to be ascribed to this infection, even where, from the habits of the patients, it might not be suspected. In Europeans undoubtedly the infection takes place *via* the mouth and alimentary tract.

Ancylostomiasis and pregnancy.—Wickramasuriya finds that hookworm disease exerts a very deleterious influence on pregnancy, and that in heavily infected districts it is the most common cause of repeated abortions and miscarriage. There is, moreover, a very heavy maternal and fœtal mortality associated with it, and early interruptions of pregnancy and neonatal deaths are also included among its effects; the combined fœtal and infantile mortality from this cause is almost 60 per cent. In the absence of skilled treatment, the chances of a successful pregnancy are remote if the hæmoglobin

percentage has fallen below 60 per cent. at the commencement of the pregnancy. Those women who are heavily infected show a predisposition to develop toxaemias of pregnancy, such as pre-eclampsia, eclampsia, and nephritic toxaemia.

Impaired renal function is an outstanding feature in the majority of expectant mothers suffering from ancylostomiasis. They must be regarded as persons with a lowered renal reserve and such cases may enter into the stage of "decompensated impairment of renal function" with the onset of gestation. There exists great danger of death from post-partum shock if the haemoglobin percentage has fallen to 30 or under at the time of labour.

Diagnosis.—Provided its presence be suspected, ancylostomiasis is easily diagnosed. In tropical countries, in patients coming from tropical countries, and in miners who work in very warm mines in cooler climates, anaemia with concurrent eosinophilia should always suggest a microscopical examination of the faeces (*see* Appendix, p. 1031). If the eggs of *A. duodenale* or of *N. americanus* are discovered, and no other reason for the anaemia is made out, the presumption is that one or the other of these parasites is responsible; at all events, no harm is likely to result from treatment based on this supposition. On the other hand, if no eggs are found it must not be concluded that the case is not one of ancylostomiasis: for it sometimes happens that, in the later stages of the disease, symptoms will persist, although the parasites which caused them in the first instance have disappeared spontaneously, or have been got rid of by treatment. The usual method of diagnosis by microscopic examination of stools for eggs does not convey a quantitative idea of the severity of the infection. The grade of infection runs from one to a thousand or more worms. Diagnosis by means of a vermifuge is much the most satisfactory method; for instance, according to Darling, where the microscopic examination revealed a 75-per-cent. infection of those examined, diagnosis by vermifuge revealed an incidence of 97 to 100 per cent. The diagnosis by means of eggs has been made much more accurate by the method of Clayton Lane, known as the floatation concentration technique (*see* p. 1031). In the majority of cases of ancylostomiasis a positive test of occult blood in the faeces is obtained, and Charcot-Leyden crystals are frequently found.

TREATMENT

General statement.—Several forms of treatment have been introduced for the killing off and expulsion of the ancylostome worms. These drugs necessarily contain a toxic principle and considerable care should be exercised in their administration. It is necessary that attention should be paid to details. The treatments will be placed in their chronological order and stress will be laid upon those considered most effective.

I. Thymol ($C_6H_3(CH_3)(OH)C_3H_7I$), was introduced by Bozzolo in 1880. It is a phenol obtained from the oils of *Thymus vulgaris* (and other plants).

It consists of large transparent crystals, slightly soluble in water, and freely soluble in fats, oils, and alcohol. The amount of thymol absorbed depends upon the presence of these substances, and death from over-dosage is caused by progressive fall in blood-pressure. Some 30–40 per cent. of the absorbed thymol is excreted in the urine.

Dosage.—An adult man, 60 gr. of thymol; an adult woman, 45 gr.; 30 gr. in pregnancy. Not to be given more than once a week. In advanced ancylostomiasis, with great debility, it must be used with great caution.

Proportionate dosage.—For children under five, 8 gr. (0·51 grm.); 5–10 years, 15 gr. (0·97 grm.); 10–15 years, 30 gr. (1·943 grm.); 15–20 years, 45 gr. (2·915 grm.).

Thymol is best given in rice-paper cachets, in three doses of 20 gr. each at intervals of an hour; the addition of an equal quantity of sodium bicarbonate or lactose aids the solution and absorption of the drug, which otherwise is apt to pass through unchanged. Before its administration the patient should be put on liquid diet for a day, and have the bowels well cleared out by a saline aperient. It should be given on an empty stomach. If the bowels do not open spontaneously within four or five hours of the last dose, an aperient should be given. Usually, by this treatment many ancylostomes are expelled and may be found in the motions. One such course of thymol may suffice; but it is well, after a week has elapsed, again to examine the stools microscopically, and, if it be found that eggs are still being passed, to repeat the course of thymol once, or oftener.

Certain precautions have to be observed in employing this drug. In some cases, after the exhibition of thymol, the urine on standing becomes dusky, almost black, and reduces Fehling on prolonged boiling; this is probably due to hydroquinone. At times thymol gives rise to a very unpleasant form of intoxication—vertigo, excitement, etc. It is advisable, therefore, for the patient, while taking the drug, to keep his bed, and to lie down for several hours after the last dose. Thymol is very insoluble in water, and is consequently, in ordinary circumstances, not readily absorbed in poisonous quantities; should, however, the patient, while thymol is present in the stomach, partake of any alcoholic drink, there is considerable risk of his being poisoned. Alcohol, ether, glycerin, turpentine, chloroform, and oils are all solvents of thymol, and must therefore be avoided when this drug is being exhibited.

The treatment of thymol poisoning consists of washing out the stomach with warm water and of giving emollients to prevent or reduce corrosion. Stimulants such as atropine, strychnine, digitalis, or strong coffee are useful in overcoming the depression of the respiratory and circulatory symptoms. Artificial respiration may have to be resorted to.

Without careful preparation by rest and judicious feeding thymol must on no account be used in advanced cases of ancylostomiasis, or where prostration is extreme. It is contraindicated in gastritis, dysentery, nephritis, and active heart disease.

II. **Beta-naphthol** ($C_{10}H_7OH$), is given in much the same manner as thymol. The dose is 3–10 gr. (0·2–0·65 grm.). It is slightly soluble in cold water (1 : 1000), more soluble in boiling water in a dilution of 1 : 75; readily soluble in alcohol, olive oil and ether. In ordinary anthelmintic doses it produces hardly any noticeable symptoms, but in bigger doses it exerts an irritative action on the kidneys and may give rise to acute inflammation. The maximum tolerated dose is 40 gr. (2·59 grm.).

III. Oil of chenopodium (*Chenopodium anthelminticum* = goose-foot, wormseed, "Jerusalem Oak," Chenopodiaceæ).—The active principle against ancylostomes or ascarides is *ascaridole* (45–70 per cent.), $C_{10}H_{16}O_2$, which is unstable, but which in 1 : 10,000 of oil kills living ascarides. It has a sharp, burning, nauseating taste, and is put up in hard gelatin capsules. The absorption of this substance is very rapid, and in toxic doses it causes depression of the respiratory centres. The excretion of ascaridole takes place mainly through the lungs. It is to be used with caution in cases with cardiac, hepatic, or visual disorders and is definitely contraindicated in pregnancy. The maximum dose of oil of chenopodium which can be given with safety is 3 c.c. in three gelatin capsules of 1 c.c. each at intervals of one hour. It is well tolerated by healthy individuals in hospital. For routine work the dose is 1·5 c.c. (24 min.) in capsules containing 3 minims (0·177 c.c.) each. Eight of these capsules should be given—in two lots of four capsules at an interval of half an hour. For children the dose should be 1 min. for each year of age up to 16. The drug should be administered three hours after a light meal. A quarter of an hour should elapse before a strong saline purge (sodi. sulph. ½ oz.) is given, with the object not only of washing the unabsorbed portion of the drug out of the intestine, but also of expelling the partially paralysed worms. Some prefer castor oil, but others consider that it tends to increase the absorption and add to the toxicity. A repetition of oil-of-chenopodium treatment should not be undertaken in less than a week.

Probably oil of chenopodium is more effective against *Necator americanus* than against *A. duodenale*. Oil of chenopodium is contra-indicated in nephritis, organic heart disease, hepatic dysfunction or intestinal ulceration.

IV. Carbon tetrachloride ($C\,Cl_4$ (*tetraform*)), a drug closely allied to chloroform, was originally introduced by Hall as a vermifuge and has been found suitable for the mass treatment of ancylostomiasis.

Carbon tetrachloride (Tetraform) is a colourless, volatile, chloroform-like liquid with a pleasant quince-like odour and of a specific gravity of 1·6. It is slightly soluble in water, and freely miscible in alcohol, oils, and other substances. When manufactured by direct chlorination of carbon bisulphide, it may contain traces of the latter drug. It exerts a preliminary burning effect on the mucous membrane, followed by anæsthetization. On exposure to light and air carbon tetrachloride slowly oxidizes, with the formation of poisonous substances, *phosgene* or *carbonyl chloride* ($C\,Cl_2$), and should therefore be kept in dark and tightly stoppered bottles. Absorption occurs from the stomach and intestines, and after large doses most of the drug is passed out in the fæces, combined with fats and fatty acids. Absorption in the body itself is by the lymphatic and portal routes, producing dizziness and drowsiness. When absorbed by the liver it gives rise to delayed toxic symptoms appearing after thirty-six to forty-eight hours. Jaundice is noted on the second day following administration. Calcium chloride in full doses has a marked effect in controlling symptoms. Acute carbon tetrachloride

poisoning closely resembles an acute abdomen, and in endemic areas of yellow fever it has been remarked that it produces symptoms reminiscent of this disease.

In ordinary anthelmintic doses the hepatic injury is not sufficient to produce noticeable effects on the liver; but after large doses necrosis of the liver develops. Continued small doses may, however, produce hepatic cirrhosis. Recent work indicates that the loss of ionized calcium and retention of guanidine are factors in the intoxication by interfering with normal metabolism. Guanidine accumulates in the blood. Indications are, therefore, for a diet rich in calcium and carbohydrates, though poor in fats and proteins. Alcohol must be avoided. In instances where any anxiety on behalf of the patient is aroused, glucose, one drachm, frequently by the mouth or in 5-per-cent. intravenous injections is indicated. Simplicity of administration is a great advantage. It is useful to administer calcium lactate in full (30-gr.) doses the day previous to treatment to increase the calcium content and so to avoid toxic symptoms. Rest in bed is not absolutely essential, though advisable in enfeebled persons. The after-symptoms are drowsiness, giddiness, and headache. Carbon tetrachloride acts directly on the helminths and will remove 95–99 per cent. of all *necators* in a single treatment, but is less effectual for *A. duodenale*.

The dose for an adult is 1 dr. (3·5 c.c.) taken in hard gelatin-coated capsules, each containing 30 min. (1·776 c.c.) of carbon tetrachloride, subsequent to a partial fast of eighteen hours without preliminary purgation. A saline purge (sod. sulph., ½ oz.) is necessary 15–20 minutes after the drug, and an enema of hot water is usually required to effect complete emptying of the bowel. The treatment is best commenced at 8 a.m. and one-half of the total dose is taken after a quarter of an hour interval. The drug can be given to pregnant women, in whom oil of chenopodium is contraindicated. The minimal dose is 3 min. (0·2 c.c.) and it should be increased by that amount for each year of age up to maturity. Many clinicians find it pleasanter and safer to give the aperient together with tetraform—i.e., tetraform 3 c.c. in castor oil (ol. ricini) 15 c.c.

It is important to note that not all the dead ancylostome worms are to be found in the first stool passed, but may continue to appear for three days after the treatment; similarly, the eggs of the parasite are held up in the folds of the intestinal mucosa and can be found in the fæces for at least a week after effective treatment has ceased.

Trichlorethylene ($CHCl : CCl_2$) in doses of one drachm (3·55 c.c.), which has a pleasanter taste and odour than carbon tetrachloride, is equally potent and safe and is given the same way.

V. Combined treatment.—It is generally admitted that the combined treatment of carbon tetrachloride and oil of chenopodium may be more efficacious than the use of either drug alone. The addition of *ascaridole* to carbon tetrachloride increases its efficiency. The two drugs mix readily. The dose recommended is 2 c.c. (min. 34) of carbon tetrachloride with 1 c.c. (min. 17) of oil of chenopodium made up to 28·42 c.c. (one fluid ounce) in liquid paraffin. The same precautions being taken, it may be given in one dose or in two halves. The Editor has used the carbon tetrachloride and oil of chenopodium treatments on two consecutive days and has had satisfactory results

from this method. The aperient, sodium sulphate, 1 oz. in a tumblerful of water, should be taken one hour afterwards. Patients continue to pass eggs in the fæces for seven days subsequent to this treatment. *Bedermin* (Bayer) is a preparation which conveniently contains both oil of chenopodium and carbon tetrachloride.

VI. Hexylresorcinol is 1 : 3 dihydroxy-4-hexylbenzol, and is a white, waxy, crystalline substance, sparingly soluble in water, but exceedingly so in alcohol or vegetable oils. Introduced as an anthelmintic by Lawson, Ward and Brown, it is given in hard gelatine capsules or crystoids.

Lampson has employed this drug and insists upon the strict observance of the following directions for the successful single-dose treatment of ascaris and hookworm infections:

Give a light evening meal consisting of soft foods only, and the following morning give the dose *on an empty stomach.* The dosage for adults and children over twelve years of age is 5 pills; for children of eight to twelve years, 4 pills; six to eight years, 3 pills; under six years, 2 pills. There appears to be no advantage in increasing these doses but smaller doses show a marked decrease in efficiency. The pills contain 0·2 grm. (3 gr.) each, and the indicated number should be taken in one dose with a glass of water. No food of any kind should be taken for at least four hours after treatment. Water may be taken freely but alcohol is definitely contraindicated. The patient may go about his usual occupation immediately after treatment and eat as desired at the end of four or five hours. A saline purge should be given twenty-four hours after treatment to remove the dead worms. The patient may continue to pass worms for as long as ten days or two weeks after this single dose and, if instructions as to food are carefully followed, one dose is usually sufficient.

Re-treatment is sometimes necessary because of reinfection or because the patient has not followed instructions as to food. Treatment should only be repeated after two weeks, if eggs are still present in the fæces. Unlike most anthelmintics, this product will eliminate successfully roundworm (*Ascaris lumbricoides*), hookworms, and, especially, threadworms.

In crystoids the crystalline hexylresorcinol is gelatin-covered. If the gelatin covering becomes broken the drug may cause irritation to the oral and œsophageal tissues. To avoid this, the crystoids *must be swallowed whole* with a glass of water; under no circumstances must the patient crush or chew them.

VII. Oil of eucalyptus 30 min. (1·77 c.c.), chloroform 45 min. (2·66 c.c.), and castor oil 10 dr. (35·5 c.c.), one-half first thing in the morning, the other half thirty minutes later, was employed by Manson as an efficient vermifuge in ancylostomiasis. It can be repeated for several days in succession, and can be used with advantage as an alternative to other treatments.

Convalescence.—The dieting of convalescents from serious ancylostome disease must, for a time, be very carefully conducted. A rich, full dietary is to be avoided until the powers of digestion have become re-established; otherwise, enteritis and diarrhœa may prove

very troublesome and retard recovery—perhaps prevent it altogether. Iron and arsenic, which may be given intramuscularly, are indicated as blood restorers.

Prophylaxis.—In devising a system of prophylaxis for ancylostomiasis, the fact that it is by means of the fæces of the already infected that the parasite is spread must be kept prominently in view. Fæcal contamination of the soil and water must therefore be prevented. The promiscuous deposition of fæces about huts, villages, and fields must be interdicted. Abundant and easily accessible privy accommodation must be provided in coolie lines, in miners' camps, in native villages, and along the highways of traffic. In the absence of a more elaborate system of conservancy, pits or trenches will suffice. They may be filled up with earth, and fresh ones opened from time to time. The Chinese plan of storing night-soil for months in large, cemented, water-tight pits is a good one. It is known that if the eggs of the ancylostome are kept in pure fæces the embryo is developed and escapes from the eggs in due course; but it is also known that unless the embryo be supplied with a certain amount of air and earth it soon dies. The thing to be avoided, therefore, is the mixing of *fresh* fæces with earth. By the Chinese system the embryos of the ancylostome are killed and, at the same time, a valuable fertilizer is secured for the agriculturist.

It is manifest that in devising privies and sanitary regulations the habits of the people they are intended to benefit must be taken into account; if native habits and prejudices are ignored, any system, no matter how perfect it may be in theory, will fail in practice.

The water supply should also be carefully guarded from all possible sources of fæcal contamination. Drinking-water, unless above suspicion, should be boiled or strained. So far as possible, facilities for removing all earth and mud from the hands and dishes before food is partaken of should also be provided and their use encouraged.

The destruction or the proper disposal of excrement is absolutely effective in the prevention of ancylostomiasis. Badly contaminated ground had better be abandoned. If this should be found impracticable, the soil should be turned over with the plough, or roasted with grass fires, or treated in such a manner that any eggs or embryos it may contain are destroyed or buried. The systematic periodical inspection of plantation coolies is to be recommended. At these inspections all subjects of anæmia or dyspepsia should be put aside for more careful examination; if the eggs of ancylostomes are found in their fæces, a judicious dosing with some of the drugs mentioned may avert serious disease in the individual, and also prevent him from becoming a source of danger to his companions.

Until a few years ago, efforts at the prevention of ancylostomiasis were directed towards treating the surface of the soil, but recent work has shown that the ancylostome larvæ spend a considerable part of their life in the deeper layers.

A most important factor underlying an efficient prophylaxis of ancylostomiasis in a community is the life-span of the infective larva during its existence in a free state in the soil. Practical experience gained by the directing authorities of the "hookworm campaign" suggests that this is much longer than experimental evidence would indicate. According to Cort, Augustine, and Payne, the life of the infective larva under these conditions does not exceed six weeks, and during that time it does not wander outside a 4-in. radius in a lateral direction, but can migrate to the surface from a depth of 36 in. This view, however, is not generally accepted. Baermann has shown that the larvæ may be recovered with ease from soil thought to be infective; the technique consists in placing the suspected soil in a receptacle, together with a quantity of water; the larvæ then rapidly migrate into the fluid where subsequently they can be easily found and recognized.

In view of the great danger to health that exists in certain countries from this and similar parasites, the sanitary authorities in such places ought to circulate among the people, by means of printed leaflets or posters, a few simple directions for the prevention of ancylostomiasis and kindred diseases. Nicholls recommended common salt as a prophylactic agent of some potency. It has the advantages of being cheap and, as a rule, easily obtainable. It has an injurious effect upon the larvæ, but requires to be brought into very intimate contact; mere sprinkling is futile. Solid salt, however, when sprinkled on fæces, does not penetrate the mass for forty-eight hours.

Clayton Lane estimated that out of 315 million inhabitants of British India, 45 million wage-earners are subjects of ancylostomiasis. Employers of labour in the Darjeeling district compute that the labourer's earning capacity when freed from this disease is increased by 25–50 per cent.

An energetic and many-sided campaign against the hookworm, already referred to, was waged in the United States, Asia, and Africa, financed by Mr. Rockefeller. State and county dispensaries for free examination and treatment of applicants were established. The total number treated in 11 States in 1912 was 238,755. A commission has been working for a number of years, and has treated 393,556 people at a cost of a little over a dollar per head. The reports issued by the Commission contain most valuable statistics, of which a few may be quoted. In Panama, in 1916, 30,094 persons were examined, and 80·4 per cent. found infected; of these, 98·2 per cent. received first treatment, and 49·9 per cent. were cured. In Antigua, of the total population, 98·8 per cent. were examined, and 29·8 per cent. found to be infected; treatment was meted out to 92 per cent. of the infected people, and 96 per cent. of these were cured. In British Guiana, out of 3,900 infected natives, only 8·6 per cent. remained as foci of infection at the end of the campaign. In Ceylon, of 4,567 tea-plantation coolies, no less than 95·6 per cent. were found infected.

It is said in the Transvaal that ancylostomiasis is rife only in the *alkaline* mines, not in the acid ones.

Darling recommended that, as the agricultural and mining population within the tropics is so universally infected with hookworm, the detection of individual infections by microscopical examination is no longer necessary. The population should therefore be treated *en masse* by an intensive method. The sanitarian should remember that an individual may be infected, yet not "affected" by the disease. Hence, apparently healthy persons may be a danger to the community.

Ancylostome Dermatitis

A form of dermatitis affecting the feet of coolies on plantations in Assam, in the West Indies, and probably elsewhere in the tropics, and variously known as ground itch, pani-ghao (Assam), water itch, water-pox, water sores, sore feet of coolies, cow itch (Queensland), sabañones (Venezuela), candelillas (Colombia), chauffie (Grenada), mazamorra (Porto Rico), is ascribed to the penetration of the skin by ancylostome larvæ, and precedes by two to four months the generalized symptoms of ancylostomiasis. The disease is of much economic importance to the planter.

The soil in the neighbourhood of coolie lines is extensively contaminated by fæcal matter. During rainy weather the ancylostome eggs in the fæcal material are hatched, and the larvæ escape into the damp earth. The bare feet of the coolies are constantly soiled with this larva-laden earth; and in this way, in many tropical plantations, Looss's experiment is unintentionally carried out on a large scale. Dermatitis, vesiculation, and it may be pustulation, or even extensive ulceration, and probably ancylostomiasis anæmia, ensue. A condition resembling larva migrans (*see* p. 852) is often produced by allied species i.e. *Ancylostoma braziliense* and *Uncinaria stenocephala* of the dog. The services of the affected coolie are lost to the planter till the irritation subsides and the anæmia is cured.

Fülleborn published the most complete account of this subject (1932). He points out that the ancylostome larvæ can only enter the skin when the soil conditions are favourable. They cannot enter through water alone, nor can they readily bore through the hard skin of the sole of the foot; less easily through the tough skin of the negro than the soft epidermis of the European. It has been shown by Khalil that the presence of a suitable host has no special attraction to the larvæ, but they are attracted by warmth (*thermotaxis*). The appearance of the skin lesions is dependent upon the number of invading larvæ. As Schüffner has shown, the inboring larvæ first form a red point, and soon a small blister forms in which the larvæ can be demonstrated in sections, and the irritation of the skin is noted after some twenty minutes. It is probable that the entrance of the larvæ also causes opportunities for the ingress of bacteria into the formation of blebs and pustules, and that this is the real "ground itch." It is by no means proven, then, that ground itch is a pure ancylostome dermatitis, for it is not found in Egypt where ancylostomiasis is rife.

Personal cleanliness and the use of some form of foot covering during the wet season, together with the prophylactic procedures for ancylostomiasis already mentioned, are the special preventive measures indicated as against this disease. Coolies working on irrigated land should be provided, if possible, with high, well-fitting boots. As regards treatment, antiseptic foot-baths and some soothing ointment are indicated. Treatment with drugs is best effected with strong salicylic solution in collodion or methyl alcohol. Barlow recommends 8-per-cent. salicylic acid in *ethyl alcohol*.

III. CESTODIASIS

The ordinary tapeworms, *Tænia saginata* and *T. solium*, and their cystic forms, are common enough in the tropics and subtropics, their distribution being regulated by the presence or absence of their proper intermediary hosts—the ox in the one case, the pig in the other, and by the habits of the people as regards cooking and conservancy.

The broad tapeworm (*Diphyllobothrium latum*) is known to occur in Norway, Sweden, Russia, Turkestan, Japan (where the natives are in the habit of eating raw fish), Lake Michigan, Madagascar, and among the natives on the shores of Lake Ngami, South Africa.

The very severe degree of anæmia, referred to with almost wearying persistence in textbooks, is not seen, in tropical practice at any rate, in association with this parasite. Cases of natural and experimental infection have been seen in whom no gross blood-changes can be found.

The only cestodes of man which, so far as is known, have any claim to be regarded as more or less special to warm climates are *Hymenolepis nana*, *Sparganum mansoni*, and *S. proliferum*.

Treatment of Tapeworm

General statement.—Preliminary starvation appears to be necessary for two days. On each of these sod. sulph. ½ oz., or castor oil ½ oz., should be given to clear out the bowel; the food should be restricted to weak tea, toast, and unlimited amounts of lemonade and glucose D. A mixture to clear the bowel of mucus is useful, such as:

Ammon. chlor.	gr.xv	(0·972 grm.)
Tinct. limon.	♏xliv	(2·6 c.c.)
Spirit. chlorof.	♏x	(0·592 c.c.)
Aq. ad	℥ss	(14·21 c.c.)

Lixen, or some preparation of senna, is preferred by some as a suitable aperient.

I. Filix-mas treatment.—Filix-mas is the rhizome of the male fern and it contains 5–8 per cent. of filicic acid (*filicin*) and a variable amount of aspidin; both these substances are anthelmintics.

Extractum filicis liquidum, dose 45–90 min. (2·66–5·33 c.c.), has a disagreeable taste and is apt to cause vomiting, so the drug is best prescribed in gelatin capsules. When prescribed in draught, it is best given with *mist. amygdalæ*, or with essential oils, *e.g.* cinnamon.

Haustus filicis maris consists of ext. filic. liq. 1 dr., syrup. zinzib. 1 dr., tinct. quillaia ½ dr., aq. menth. pip. to one ounce.

The capsules contain 15 min. each of the liquid extract. The dose of these is one to six, according to the age of the patient. It is effective against *Tænia saginata*, *T. solium*, and especially against *D. latum*. The most difficult species to dislodge are *T. saginata* and *Hymenolepis nana*. On the morning of the treatment the patient should have a small cup of tea. For a fully adult man the full dose of filix mas is 1½ dr., for a female 1 dr. For specially resistant cases the Editor has prescribed up to 120 minims (2 dr.) with safety. It is given as follows :—

At 8 a.m. two capsules of 15 min. of filix mas.
8.30 a.m. repeat.
9 a.m. repeat.

The patient must then lie perfectly quiet and take nothing but a few sips of water. At 10.30 a.m. half an ounce of sod. sulph. should be given. The bowels being opened freely by the salts, segments of the tapeworm should soon appear : all motions should be saved and strained to search for the head ; should this not be seen, a soap-and-water enema should immediately be given. Very often, however, the head is not found and it may be passed separately several days after the cessation of treatment ; therefore failure to demonstrate the head does not necessarily indicate that the patient is not cured.

Some authorities reinforce this treatment with a mixture containing oil of turpentine 20 min. emulsified with mucilage of acacia, or with a eucalyptus oil mixture containing 15 min. (0·88 c.c.) of eucalyptus.

Sitting upon a night commode containing steaming hot water is said to entice the tapeworm down the bowel and render the head more easily detachable. The patient must rest in bed the whole day when undergoing treatment.

Oleoresin of aspidium (U.S.P.) contains *filicin*, the anhydride of filicic acid. To be successful the oleoresin should have been recently prepared. The patient should fast the day previous to treatment. At 6 p.m. on that day 30 gr. of mag. sulph. are given, and again on the morning of the treatment a similar dose. No breakfast should be taken, and after the bowels have been opened ½ oz. of the following emulsion is administered.

Oleoresin of aspidium . .	ʒi	(3·89 grm.)
Pulv. acac.	ʒss	(1·944 grm.)
Aq. dest. ad	℥i	(28·42 c.c.)

An hour later a second dose of ½ oz. is given, and after a further interval of two hours, a soap-and-water enema.

Intraduodenal treatment of tapeworm.—Sawitzky recommends 30 grm. sod. sulph. in the afternoon, and the patient should be starved for the rest of the day. Next morning the bowels are opened by an enema, the patient swallows a catheter and is placed on his right side. Penetration of the catheter into the duodenum takes place in 1–2 hours. He is then turned on his back, and a small glass funnel is attached to the catheter. An emulsion of ethereal extract of male fern 50 grm., gum arabic mucilage 5 grm., sodium bicarbonate 0·5 grm., distilled water 50 c.c., is prepared. About three-quarters of this amount, equivalent to 3–4 grm. (50–60 min.) male fern, is introduced ; immediately 50 c.c. (1¾ oz.) of warm 50-per-cent. solution of sodium sulphate is poured in and the catheter extracted. Expulsion takes place in two hours.

II. Pelletierine.—Commercial pelletierine is a mixture of two alkaloids, pelletierine and isopelleterieue, and is obtained from the stem and root bark of the pomegranate (*Punica granatum*).

Pelletierine tannate, a mixture of the tannates of the alkaloids, is a light yellow powder, slightly soluble in water (1 : 700), but soluble in 90-per-cent. alcohol (1 : 80). The dose is 7 gr. dissolved in alcohol, followed two hours later by castor oil 1 oz. ; a soap-and-water enema may be necessary.

Pomegranate bark is an infusion of the root bark of *Punica granatum* : 150 grm. are infused for twelve hours in a litre of water and then boiled down to half, and can be given by the mouth or be passed into the duodenum by Einhorn's tube. Before use the decoction is warmed to 100° F. and three doses of 65 c.c. (ʒ xviii) each are given at half-hour intervals, followed by a saline purge, after which the catheter is withdrawn.

III. Melon seeds.—These are obtained from *Curcubita maxima*, a native of the Levant. For medicinal use they should not be more than a month old and should be deprived of their seed-coats. They do not kill the tapeworm, but when followed by a saline purge, they do bring it away. The dose is 700 grm. for an adult, and the bruised seeds may be mixed with honey or milk, or with stewed fruit, and given on an empty stomach in the morning at 6 a.m. At 8 a.m. 3 oz. of *mist. alba* are given. This is the average dose for an adult.

IV. Areca nut.—Areca nut (*Areca catechu*) is used in China. The dose is 30 grm. of powdered betel, boiled for thirty minutes in 200 c.c. of water and taken on an empty stomach.

V. Sostol (Bayer), a soluble yellow crystalline powder, is the hydrochloride of an acridine compound, and is said to be specially efficacious in Diphyllobothrium and Hymenolepis infections. The usual preparation is required. Sostol pellets are given early in the morning on an empty stomach, and adults receive 6 pellets of 0·1 grm. (1½ gr.), followed three hours afterwards by castor oil or a saline aperient. Children up to four years of age should take 1–2 pellets and children of from five to eight, 4 pellets.

VI. Alternative treatment.—*Carbon tetrachloride* anæsthetize

tapeworms and, especially when combined with *oil of chenopodium* aids in their expulsion. It is combined in the following mixture

Carbon. tetrachlor.	ʒi	(3·5 c.c.)
Ol. chenopod.	♏xv	(0·88 c.c.)
Paraff. liq.	℥i	(28·42 c.c.)

This should be given in two doses as in ancylostomiasis. Adults should receive the full dose; children under six, 2 dr.; up to eight, 3 dr.; up to fourteen, 4 dr. The mixture should be made up fresh daily. Half an hour afterwards the patient should be given a saline aperient, or *pulv. jalap. co.* 1–2 dr. (3·55–7 c.c.) may be used. The Editor has had the best success with this treatment in the case of *T. solium*. *Hymenolepis nana* (*see* p. 927) is extremely difficult to dislodge.

After-treatment.—In those not infrequent cases in which the whole of the tapeworm, including the head, is not removed, efforts should be made to prevent the further growth of the helminth. A substance called *Helminal*[1] (Merck), made from a marine alga, is now on the market and should be given in three tablets three times daily for three days. For children and infants a granular form is put up, a small teaspoonful, three times daily, being sufficient. *Beta-naphthol* 15 gr. (1 grm.) (*see* p. 814) in tablet form should be taken first thing in the morning on an empty stomach for ten days. *Pymosel*, which contains 20-per-cent. *Pyrethrin* and is made by Vermènes, Paris, is specially suitable as a vermicide for children. The dose is one teaspoonful before breakfast, and can be repeated for ten days.[2]

IV. CYSTICERCOSIS

Though the cysticercus, or bladder-worm stage of *Tænia solium*, normally develops in the pig and infection of man takes place by eating pork, which contains the larval *cysticerci*, yet occasionally man himself may serve as the intermediate host through the accidental ingestion of the eggs of *T. solium*. The embryos may migrate to almost any organ, especially the muscles of the tongue, neck, or ribs and sometimes the lungs, liver, or heart, and they have actually been removed from the eye. One of the most striking recent contributions to medicine has been the demonstration by MacArthur that the embryos show a peculiar predilection to invade the brain. It has been known for some time that individual cases of cysticercosis may be accompanied by epileptic seizures; but it has only been recently recognized that the frequency of epilepsy in the British Army, especially in soldiers who have served abroad, is due to cysticercosis of the brain. The onset of epileptic seizures in a previously normal adult after, or during, service abroad should suggest this possibility. The possible extent of indigenous cysticercosis in England is, however, unknown. One of MacArthur's cases contracted the infection in England.

Recent investigations on epilepsy in young, and otherwise healthy, soldiers with good antecedents, has shown that cysticercosis is the cause. Out of one batch of 22 cases investigated by MacArthur ten were proved to suffer from cysticercosis. In another 82 cases in British soldiers, evidence of infection with *Tænia solium* was obtained in 22.

[1] This can also be used in ascariasis.
[2] Harwood, Chemist, Watford, Herts.

In some instances the fits commence about the time the cysts are first detected ; in others there may be a quiescent period of some years between the appearance of the cysts and the first epileptic seizure, or in other instances the cysts may become palpable subsequent to the onset of epileptic fits. The number of palpable cysts varies widely in different cases. Large ones which have been under observation for years may vanish in a few days. The larger ones usually contain dead larvæ and the cyst capsule is tense owing to the large amount of contained fluid. The death of the larva is in some way associated with an increase of this.

Pathology.—In the brain the cysticercus becomes enclosed by a wall of neuroglia ; small round cells and a few plasma cells are present between the delimiting neuroglia and the surrounding normal brain tissue. When alive, the cysticerci enjoy a relative tolerance on the part of the host, but after death they act as foreign irritants ; the tissues surrounding dead and disintegrating cysticerci undergo active degenerative changes with a marked cellular response. To the naked eye the degenerating tissues may be visible around the cysticercus as a discoloured ring, and later, if the patient survives, they undergo necrosis. This dead area, which may extend 5 mm. beyond the cysticercus, is ringed off from the normal brain by a wall of sclerosed neuroglia.

After a variable period determined in part by the resistance of the host, the parasites die and often undergo calcareous change. Calcification commences in the scolex, while the cyst capsule and its contents are unaffected. Calcification may stop at this point, and the cyst-wall may collapse through the escape of the fluid, or the collapsed cyst may be flattened out by pressure of the surrounding muscles and calcify in an extended form. Apparently a period of three years is necessary after the death of the cysticercus for the scolex to calcify. Calcification of the cysts in the brain takes a much longer time to complete.

Symptoms.—The fits themselves may resemble those of the Jacksonian type, with cyanosis, biting of tongue, and involuntary passage of urine. In some instances, again, they are irregular in type and cerebral tumours may be suspected. Nervous symptoms other than fits may be produced ; thus the initial clinical picture may be that of disseminated sclerosis, or of cerebral tumour. Psychical states may be produced, with cerebral irritability and loss of memory.

Usually the process of invasion with cysticerci gives rise to no general reaction, but the infected subject notices the gradual development of small subcutaneous or intramuscular swellings. More rarely, a general toxæmia with pyrexia develops. Sometimes, too, the localized intramuscular swellings resemble a muscular dystrophy. Again, cysts may be present in large numbers without the patient's knowledge until they are discovered accidentally by radiological examination. As a rule, there is no ascertainable history of tapeworm infection ; though in one case the first fits commenced during treatment in hospital for this disease. There may be a history of incomplete fits, often regarded as hysterical, and every degree from petit mal to Jacksonian epilepsy. Intense headache may be the one symptom preceding a fatal attack. Psychical disturbances may appear and melancholia, or acute mania, dominate the picture.

Diagnosis.—The most helpful sign in diagnosis is the development of palpable cysts in the tissues, and these may number from one to thirty or more. The cysts themselves may be the size of a hard pea, a hazel-nut, or even a pigeon's egg. Their situation varies enormously; they have been found in the lips, masseter muscles, neck, chest, abdominal walls, back, and groin. Cysts, if not numerous, are easily overlooked. Indeed, unless evidence of cysticercosis is systematically sought for, the diagnosis may be missed, as the nodules may be absent at the time of the examination, only to come out in crops at a later date. The radiological evidence may not be convincing for some years, as calcification does not take place for four or five years after infestation.

After a time of very variable length, the contained larva dies and becomes calcified—a process which commences in the parasite itself and then extends to the cyst-wall. Usually the larva becomes calcified during a period of four to five years. In order to demonstrate it, a suitable cyst is excised under local anæsthesia and the host capsule is enucleated, so as not to injure the cysticercus. The appearance of the translucent membrane with its central "milk spot" is characteristic. If alive, the parasite may evaginate the head and neck, or it may be induced to do so by immersion in hot saline.

When the parasite has calcified, a good skiagram will show it as a small elongated shadow, but the completely calcified cyst gives a very characteristic appearance (Plate XXVIII). Evidence of calcification within the brain has been demonstrated in five cases. Unfortunately the eosinophile cell is no aid to diagnosis, as in no cases so far investigated has an increase been noted. Complement-fixation tests have proved disappointing, and it has been shown that a negative test does not exclude the possibility of infection, and the intradernal Casoni test is positive in about 50 per cent. of cases. Trawiński has developed a precipitin test, using an antigen made from *Cysticercus cellulosæ*.

Apparently no prophecy can be made upon the duration of the epileptic symptoms. Sometimes the epileptic seizures cease without apparent cause; in others they persist for eight years or more. There have been several fatal cases in which the cysts have been found to be limited to the brain. There are no constant changes in the cerebro-spinal fluid.

Treatment.—Intravenous injections of antimony tartrate have been tried out, but often without much effect, and although instances of successful localization and removal of single cerebral cysticercal cysts have been recorded in the literature, usually such an interference is unjustifiable. Luminal and bromides are helpful in controlling fits. Observation on tissue changes which follow the death of intracerebral cysticerci would suggest that destruction of large numbers of these parasites might only make matters worse.

In actual practice temporary amelioration of symptoms after removal of one or more cysts has often been followed by the death of the patient.

Prophylaxis.—This cannot be undertaken until the source of the infection has been ascertained. It is commonly believed that human cysticercosis is an accidental complication occurring in the host of an adult tapeworm, the auto-infection being caused by the ingestion of eggs or possibly by regurgitation of segments into the stomach. Much more probable is it that the infecting eggs are conveyed from some extraneous sources in much the same manner as are the cysts of *Entamœba histolytica*, and it is possible that the infection is acquired in some way from pigs, either by eating sausages made from the intestines, or through some contamination by pig's excreta.

Section X.—DISEASES DUE TO POISONS, INCLUDING SNAKE-BITE, AND INFECTION WITH DIPTEROUS FLIES AND LEECHES

CHAPTER XLV

VEGETABLE POISONS

An exhaustive account of the various poisonous plants, their uses and antidotes, is beyond the scope of the present work. All that can be done is to indicate those of most importance to the tropical practitioner.

POISONS USED FOR CRIMINAL PURPOSES

Of inorganic poisons, the one most generally used by tropical races is arsenic in some form, cleverly intermingled, as a rule, with flour, or even inserted into the grains of maize or millet, or introduced into sweets, as in Egypt; in Malay, powdered croton seeds or datura are used. Native races usually possess a much wider and more intimate knowledge of organic poisons than do civilized peoples.

In Brazil, common native poisons are derived from *Paullinia pinnata*, which contains an alkaloid, *timboin*, and from the fruit of *Theretia ahonai*, of which the active principle is *theretosin*; both of these excite vomiting and cause respiratory failure.

In the Dutch East Indies a poison extracted from the roots of *Milletia sericea* is employed, which produces debility, headache, diarrhœa, collapse, and death.

In the Pacific islands the native poison is obtained from the fruit of *Barringtonia speciosa*.

In India a large number of vegetable poisons are in use. In the Madras and Bombay Presidencies an extract is obtained from the roots of *Nerium odorum*, the white oleander, which contains two glucosides having a specific action on the heart. Similar substances, *urechitin* and *urechitoxin*, derived from *Urechites suberecta*, exert a cumulative action, and therefore sudden death may take place without suspicion of poisoning being aroused.

The juice of an *Asclepias* is used in India as an infanticide; the symptoms induced are vomiting, salivation, and cramps. The roots of various species of aconite (*A. ferox*, etc.) are used for the same purpose; death is said to take place rapidly—in three to six hours, as a rule. Several species of Apocynaceæ, such as *Cerbera odollam* and *Thevetia neriifolia*, the sap and seeds of which contain a glucoside, *thevetin*, are very deadly—death from cardiac failure taking place in from twelve to fifteen hours. In Southern India,

Burma, and Ceylon a decoction of the fruit of the *Gloriosa superba*, one of the Liliaceæ, allied to squills, is employed for criminal and suicidal purposes. The active principle, *superbin*, causes gastro-intestinal irritation and cardiac failure within four hours. The commonest poison in India and Ceylon is the datura, one of the deadly nightshades, of which there are several species. The seeds, mixed with food or drink, produce a state of extreme mental exaltation, followed by coma ; the active principles are *atropine*, *hyoscyamine*, and *scopolamine*.

In Africa the leaves of *Hyoscyamus fahezlez*, containing *hyoscyamine* and *scopolamine* as active principles, are used by the Tuaregs of the Sahara. On the West Coast, a decoction of a cactus, colloquially known as " oro," produces blisters in the mouth, vomiting and gastro-intestinal irritation, collapse, and death within a few hours. In China, opium is the poison most frequently used, especially by women, for suicide.

DISEASES DUE TO THE INGESTION OF POISONOUS FOODS

Lathyrism

This disease, characterized by various nervous manifestations, such as ataxy, spastic paraplegia, weakness, and muscular pains, without any psychical disturbances, occurs in Abyssinia, Algeria, and India in those districts in which vetches, " Khasari," *Lathyrus sativa* and allied species, form the main article of diet. A similar disease occurs in animals fed upon the same food. The arms and trunk are seldom involved ; incontinence of urine and sexual impotence are early and common symptoms. The disease is very chronic and seldom ends fatally. Weeds which contaminate the true khasari, such as " akta " (*Vicia sativa*), contain bases with alkaloidal properties such as *vicine* and *divicine* ; the latter in combination with a glucoside produces, on inoculation into guinea-pigs, a fatal disease.

Atriplicism

A combination of curious cutaneous and nervous symptoms is known in China under this name. It is an intoxication caused by ingestion of the leaves of *Atriplex littoralis*. The earliest symptoms consist of great itching of the hands, followed by œdema, and often by bullæ as well ; the finger-tips may become gangrenous, cutaneous hæmorrhages may occur, and the face and eyelids become cyanotic and œdematous. In many ways the condition resembles Raynaud's disease and erythromelalgia. Yu Ky has described a condition after eating the leaves of *Atriplex serrata*, or *Chenopodium hybridum*, in which the symptoms and signs are similar to the foregoing, and it is considered that the skin lesions should be ascribed to a light-sensitive dermatosis.

Ackee Poisoning (Vomiting Sickness of Jamaica)

An acute and very fatal condition, locally termed " the vomiting sickness," has been known for many years in Jamaica. It is found principally in rural districts and occurring in what were regarded as circumscribed epidemics. The causation and nature were neither apprehended nor understood, although several Commissions had attempted their elucidation. To Dr. Harold Scot

belongs the merit of clearing up the mystery, and indicating simple and practical methods of prevention, which, if effected, has averted a considerable mortality, particularly among children. It is estimated that since 1886 over 5,000 lives have been lost in Jamaica from this cause alone.

The vomiting sickness is confined to the West India Islands, practically to Jamaica, and occurs principally in the cooler months, from November to April.

Symptoms.—A previously healthy child suddenly complains of abdominal discomfort, vomits several times, apparently recovers, and perhaps falls asleep. Three or four hours later, vomiting—now of a cerebral type—recurs.

Fig. 168.—Ackee fruit. ¼ nat. size. (*Photo: Dr. G. M. Vevers.*)

Within a very short time, a few minutes perhaps, convulsions and coma supervene; and death follows, on an average, about twelve hours from the oncoming of the initial vomiting, though it may occur in as short a period as one and a half hours. The case-mortality amounts to 80–90 per cent. In those who recover, convalescence is complete in twenty-four hours.

During the attack the temperature is normal or subnormal, rarely rising to 101° F.; the pulse is 90 to 100; the respirations are 26 to 30, sometimes, as death approaches, being of the Cheyne-Stokes type. The pupils are slightly dilated and, until near the end, react to light, etc. Unless during the convulsive seizures, there is no muscular rigidity. Post-mortem examination reveals hyperæmia of viscera with a tendency to minute intestinal hæmorrhages, together with marked fatty changes, especially in the liver and kidneys, and sometimes to a less degree in the pancreas and heart-muscle.

Ætiology.—Scott has shown, on what must be regarded as convincing evidence—clinical, seasonal, epidemiological, and experimental—that the vomiting sickness is really the result of poisoning by a fruit, much used by negroes in Jamaica, called *ackee*, the fruit of *Blighia sapida* (Fig. 168), a tree very common in the island. A similar fruit is found on the West Coast of Africa, where it is known as *Isin*. When mature and in good condition, this fruit is wholesome enough ; if gathered before it is quite ripe and before it has opened while on the tree, or if gathered from an injured branch, or opened after falling on the ground, it is poisonous. It would appear that the poisonous element in the immature and unsound fruit is soluble in water, for the " pot water " in which the ackees have been cooked is much more toxic than the cooked fruit ; and, further, that the poison is precipitated by alcohol. Jordan and Burrows have shown that the toxic principle is also contained in the seeds and in the arilli of the ackee which have not yet " opened " in the natural way. The nature of the toxic principle has not yet been ascertained.

Treatment.—An emetic, and washing out the stomach with an alcoholic fluid during the primary vomiting, seem to be indicated. Scott is insistent that the administration of alcohol must be prompt.

Prophylaxis.—When the fruit in various stages falls to the ground, only the opened pods, that is the ripe fruit, should be used for food. The immature unopened pods should all be destroyed.

Manioc Poisoning

Manihot aipi (sweet cassava) and *Manihot utilissima* (bitter cassava) are ground roots extensively used in the West Indies. From the latter are produced starch, tapioca, and cassava cakes. Poisoning by the latter arises from the failure to remove the contained glucoside and enzyme. In the presence of water these release free hydrocyanic acid, and nausea, vomiting, distension of the abdomen, and impeded respiration result.

Nami (*Dioscorea hispida*, Dennst, and *D. hirsuta*, Bl.) is a colloquial term for a species of yam, employed for food in parts of the Philippines. Its use has frequently caused food poisoning, and occasionally it has been put to criminal purposes. An alkaloid—*dioscorine*—has been obtained from the full-grown tubers.

Coral Plant (*Jatropha multifida, L.*)

Coral-plant poisoning has been reported by Raymond from Tanganyika, the symptoms being colic, cramps and thirst, with a subnormal temperature. Two species, *J. curcas* and *J. glandulifera*, are common in the West Indies. *J. glandulifera*, since it grows rapidly, being used in Jamaica for fencing compounds. The nuts taste very like sweet almonds, and the plants are known as " physic nuts " ; a third species, *J. multifida*, is known as the " French physic nut." *J. gossipyifolia*, which occurs in the West Indies, is known as the wild Cassava, or " Belly-ache bush," and its seeds contain an intestinal irritant like croton oil. A fifth species, *J. urens*, from the same area, bears leaves provided with stinging hairs, which cause itching, smarting, flushing of the face, swelling of the lips and faintness. Recovery is rapid after ejection of the poison by vomiting.

Jenghol Poisoning

Jenghol poisoning (Djenkol) occurs in Java from eating a bean, *Pithecolobium lobatum*, and has been described by de Langen, Hijman and Van

Veen. Djenkol acid is believed to be responsible. The symptoms are chiefly pain in the renal regions, dysuria, and often anuria. The urine frequently contains blood-casts, and sharp acid crystals, the chemical composition of which has been worked out. The presence of these crystals in large numbers in the urethra causes necrosis, fistula, and extravasation. The jenghol bean has a high vitamin-B content and is used as food in spite of its toxic properties. The eating of these beans by normal persons is followed by an increase in the excretion of sulphur.

Datura Poisoning

Various plants belonging to the order Solanaceæ are used in many parts of the tropical world to produce unconsciousness. The seeds of *Datura fastuosa* are used by Thugs in India for this purpose, but datura poisoning is by no means confined to India. The seeds have only a slight taste and are consequently easily introduced into food; their intoxicating properties are widely known. *D. sanguinea* is used in Peru and Colombia, and *D. ferox* and *D. arborea* in Brazil. The characteristic seeds are found in the fæces and, in fatal cases, in the small intestine.

Manchineel Poisoning

The manchineel, or manchineale (Sp., *manzanilla*), *Hippomane mancinella*, belongs to the order Euphorbiaciæ and is a tree distributed along the coast-line of North, South and Central America and the West Indies. It is particularly common in Barbados, the Grenadine Islands, and the Archipelago of Les Saintes, in French West Indies. Two varieties are recognized, one with "holly" and one with "laurel" leaves; both are equally toxic. The first, which resembles a crab-apple, has a pleasant odour.

The latex contains a greenish resin, which is the active toxic principle. Like the Upas tree, the manchineel has been said to bring death to those who sleep under its shade. All parts of the tree are toxic, but the amount of latex in any portion varies with the season; even the dry wood and sawdust are endowed with irritant properties. Hypersensitive people who pick the manchineel apples (or fruit) may suffer from a skin eruption, erythema, bullæ and vesiculation appearing. The toxic dermatitis is especially liable to affect the genitalia and the anus, causing a vesiculo-pustular eruption which may be confined to the corona penis. A conjunctivitis with pain, photophobia and blepharospasm may result from the introduction of the latex into the conjunctival sac. The severe dermatitis brought about by handling the dried wood-powder is thought to be an allergic manifestation.

If the fruit is eaten, as it may be, by ignorant visitors, children or insane people, vesiculation of the buccal mucous membrane with diarrhœa and blood-and-mucus stools may ensue. Fatal poisoning may result.

As regards treatment, it is recommended that manchineel juice on the skin should be washed off with sea-water. Blisters should be kept aseptic, and if extensive should be treated like a second-degree burn. When the fruit has been eaten, emesis should be induced.

Alcoholism and Drug Habits

Alcohol poisoning occurs in varying degrees among nearly all native races, and in its symptoms and course does not differ materially from alcoholism in other parts of the world. Rum (65–72 per cent. of alcohol), obtained

from the fermentation of molasses, is used in the West Indies and South America; arrack (50–60 per cent. alcohol) is manufactured in India, China, and Java from fermented rice or from palm sap; while a slightly fermented drink known as toddy is obtained from sweet sap of various palms, and is drunk in India, Ceylon, and West Africa. In South America a potent alcoholic drink is made of the fermented juice of *Agave americana*, and is known as "pulque."

Opium poisoning.—The opium habit, either as eating or as smoking—the symptoms of which are too well known to require description—is common throughout the tropics. Opium poisoning is also a favourite form of suicide, especially among women.

Cannabis indica.—Indian hemp, or *hascheesch*, grows in India, Persia, and Arabia, and is a variety of the common hemp, *Cannabis sativa*. The leaves are powdered down, and either chewed or smoked as a preparation known as *bhang*; an extract of the flowers is known as *ganga*. Both these preparations cause great nervous excitement and, if persistently used, often lead to permanent insanity, the main features of which are hallucinations and illusions. Hascheesch in its various preparations, often with the addition of extracts of various Solanaceæ, such as datura and nux vomica, is habitually taken daily by millions of the inhabitants of Africa and Asia. The most stringent Government regulations have been framed with a view to suppressing trade in this drug.

Kawa or yangona, the powdered root of one of the Piperaceæ, prepared so as to form a beverage, is drunk on festive occasions throughout Polynesia. Formerly the root was masticated by specially selected girls previous to the final steps in the preparation of the drink, a practice which was a prolific source of tuberculosis, and on that account prohibited. Over-indulgence in kawa induces a state of hyperexcitement, with loss of power in the legs. Chronic intoxication induces a condition of debility, with coarse roughened skin.

Betel.—The chewing of betel, the leaves of *Piper betel*, together with lime and areca nut (*Areca catechu*), is a common practice in India and Ceylon, and generally throughout the East. The mouth, lips, and teeth are stained a bright-red colour. It produces a flushing of the face, has a mild stimulant and possibly anthelmintic properties. In Central Africa the nuts of the kola tree (*Sterculia sp.*) are chewed habitually, and act, like betel, as a muscular stimulant, without, it is said, producing any detrimental effects.

Epidemic Dropsy (Mustard-oil Poisoning)

Synonym.—Famine Dropsy.

Definition.—Epidemic dropsy is a disease somewhat resembling beriberi. Clinically, it is characterized by dropsy associated with cardiac symptoms, but without marked paralysis or anæsthesia.

History and geographical distribution.—This disease was first noted in Calcutta in 1877; it has since occurred there sporadically, but vanishes in the hot season. In Mauritius in 1879, it affected one-tenth of the coolies, of whom a large number died. An epidemic broke out in Fiji in 1926 and was curiously limited to Asiatics; no native Fijians were attacked. In Purulia (Nagpur, India) there have been epidemics at intervals since 1913, the worst being in 1934, when over 2,000 persons were attacked.

Ætiology.—In spite of the apparently wide distribution of epidemic

dropsy most of our information comes from India, where the disease evinces a remarkable predilection for the Hindus, especially for the female sex. Children under puberty are less liable than adults; sucklings are seldom affected. The weak and the robust are equally susceptible. It has been remarked that very few of the victims are of the poorer class, nearly all coming from the middle and upper classes. No infantile form of this disease has been described.

Greig, who made a special study of the disease during the epidemics in Calcutta concluded that in many ways epidemic dropsy resembled ship beriberi, while observations on war œdema seemed to indicate that a diet deficient in fats played the chief part; others, again, regarded the disease as due to a deficiency of calcium salts. Diminution of the circulating protein, by decreasing the osmotic pressure, may lead to œdema of the tissues, as Eckstein has demonstrated in the œdema of chronic parenchymatous nephritis. In epidemics of beriberi the absence of nerve symptoms is the exception—in fact, is very rare, and always concurrent with other cases in which nerve symptoms are pronounced, and with purely atrophic cases; such have not been seen in the Calcutta or the Mauritius epidemics. Some modern observers in India, especially Acton and Knowles, Sarkar, Gupta, Megaw, and Banerji, attributed the symptoms to intoxication caused mainly by rice which has been damaged from faulty storage. Recently it has been commonly suspected that some abnormal ingredient of the food is the cause.

An outbreak in Fiji in 1926, which was confined to the Indian population, was attributed to mustard oil used in the preparation of curries, and later, Banerji and Ghosh in Bengal came to the same conclusion. Strong support for the mustard-oil theory has recently been brought forward by Lal, Roy and Ghosal in Calcutta. In 1935–6 they made a house-to-house enquiry in seven different centres where outbreaks had occurred, and they found that the disease had afflicted many middle-class adults, especially Bengalis and those who adopted the same habits, and there was no evidence that rice *per se* had any bearing on the disease. Bengalis, who were most susceptible, are the main consumers of mustard oil and it was found that there were no cases among non-consumers of the oil and that the incidence of epidemic dropsy increased with the amount consumed.

Experiments among volunteer convicts in Calcutta jails showed that all six persons who were given "suspected oil" developed the characteristic symptoms after five or six days, while the controls remained healthy. This work supports the view that the disease is due to some substance, probably a chemical poison, occurring in *some* consignments of mustard oil.

According to Hawes, the essential substance in mustard-oil poisoning is *allyl-isothiocyanate*, and the changes in the oil take place when it is cooked at a high temperature. Confirmation of this is to hand from the experiences of Landor and Williams in Singapore, where they observed three cases, all living in the same house, who had partaken of the same mustard oil. Lal and Roy in Calcutta have found that the "mustard-oil theory" is popular among the lay people, and they conducted feeding experiments on 12 healthy young subjects. On

the fifth day, symptoms were noted, consisting of fever with œdema of the legs.

Pathology.—De describes extensive vascular dilatation in the deeper layers of the skin, and this is regarded as a characteristic feature of the disease. The heart-muscle shows no degenerative changes, but there is thinning of the muscle-walls and the muscle fibres are separated by dilated capillaries; similar changes are present in the ciliary body of the eye, leading to excessive fluid in the anterior chamber. Shanks also finds capillary dilatation wherever the vessels are least supported, and this is most obvious in fatty tissues, whether subcutaneous, subpericardial or subperitoneal. Similar changes are seen in the lungs, in the cervix uteri, in the ovaries and in the intestines. The liver usually presents a "nutmeg" appearance (Shaha). In Fiji the vascular outgrowths resembled sarcoids and bled profusely, but it has been pointed out that they are not true sarcoidal growths. The chief changes occur in the blood-vessels, which are dilated and surrounded by proliferating endothelial cells. It is the formation of new capillaries which brings about the resemblance to sarcoids.

Chatterjee and Halder state that in an average case the total erythrocyte is about 3·8 millions, whilst the hæmoglobin is reduced to 11 grm. per 100 c.c. As regards the differential count, the lymphocyte percentage is raised and there is usually a considerable eosinophilia. The reticulocytes are not increased as a rule.

Symptoms.—Dropsy is almost invariably present. It usually appears first in the legs, and in some instances is confined to the lower extremities; in others it spreads and involves the entire body. Occasionally it is very persistent, recurring during convalescence. Fever also is very constant; sometimes it precedes, sometimes it accompanies, sometimes it follows the dropsy. It is rarely high, ranging usually from 99° to 102° F. Diarrhœa and vomiting generally ushered in the disease in the Mauritius epidemic. In Calcutta these symptoms were not so frequent, although by no means rare there, occurring at both the earlier and later stages. The total duration of the disease is about six weeks.

Peripheral neuritis is absent and the knee-jerk is not abolished, but usually distressing aching of muscles, bones, and joints are prominent features. An exanthem, erythematous on the face, rubeolar on the trunk and limbs, was frequently seen in Mauritius, less frequently in Calcutta. It appeared about a week after the œdema, and lasted from ten to twelve days. On the skin vascular nævi often appear and may bleed profusely, while telangiectases are commonly present. De and Chatterjee describe the eruptions as "nodular" in some epidemics, this having been the dominating feature, while nodules on the mucous membranes have been noted. They do not inconvenience the patient, but may bleed uncontrollably. Ecchymotic patches consist, not of hæmorrhage, but of telangiectases. Three to six weeks after the first symptoms, nodular excrescences are found; in number they may be

100 or so; they may be sessile or pedunculated, varying in size from that of a pea to a lemon, and they readily bleed (Fig. 169.)

Disturbances of the heart and circulation are prominent features in nearly all the cases. The pulse is weak, often rapid and irregular, the blood-pressure low: cardiac bruits were noted. Breathlessness on exertion occurred in all cases, severe orthopnœa in many. Signs of pleural and pericardial effusion, of œdema of the lungs, of pneumonia, and of cardiac dilatation are common. Hawes states that the lung

Fig. 169.—Nodular lesions in epidemic dropsy. (*After De and Chatterjee.*)

signs are characteristic and are almost like a bronchial spasm with defective aëration. Anæmia is usually present and marked, and so are wasting and prostration. The urine is not albuminous, but of low specific gravity, and greatly increased in amount. Concurrent glaucoma is not uncommon.

Diagnosis.—The differentiation of epidemic dropsy from war œdema noted in Central Europe and Egypt during the Great War may be difficult. The latter occurred in a population undergoing dietetic restrictions, and was characterized by great emaciation and a high degree of anæmia. Experiments on rats with diets deficient in proteins

and salts have produced a condition not unlike nutritional œdema. From œdematous beriberi the disease is differentiated by the pyrexia and the very peculiar erythematous rash, and the persistence of the deep reflexes.

Treatment.—An analysis of the albumin-content of the blood will serve as an indication for the administration of albumin by the mouth. Egg- and milk-albumin are indicated in large quantities if such a deficiency is demonstrated. Treatment then should be directed to giving a liberal protein diet and substituting wheat bread for rice. Thyroid extract is said to be useful, and tincture of ephedra, 20–30 min., with calcium lactate 10 gr. three times daily, is valuable.

CHAPTER XLVII

ANIMAL POISONS

Poisonous Snakes

Snakes form a sub-order of the reptiles which have definite characters. The quadrate bone is articulated to the skull, but there is no tympanic cavity. The brain-capsule is osseous, and the mandibles are united mesially by a highly elastic ligament. The limb girdles are absent or reduced to mere vestiges. A peculiar feature is that there are no movable eyelids, but the eyes are covered with a transparent disc, which is shed with the rest of the epidermis. The tongue is deeply bifid and is retractile into a basal sheath; but is protrusible when

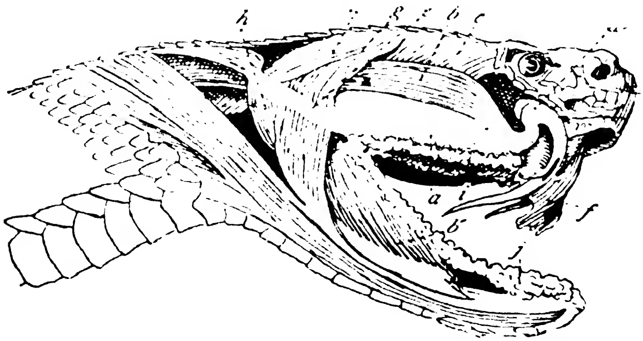


Fig. 170.—Poison apparatus, venom gland, and muscles of rattlesnake (lateral view). (*After Duvernoy, in Boulenger's "Snakes of Europe."*)

a, Venom-gland; *a'*, venom-duct; *b*, anterior temporal muscle; *b'*, mandibular portion of same; *c*, posterior temporal muscle; *d*, digastricus muscle; *e*, posterior ligament of gland; *f*, sheath of fang; *g*, middle temporal muscle; *h*, external pterygoid muscle; *i*, maxillary salivary gland; *j*, mandibulary salivary gland.

the mouth is closed through a notch in the rostral shield. As in the lizards, the anal cleft is transverse.

The poison apparatus consists of a pair of venom-secreting glands connected by ducts to the poison-fangs in the maxillæ; they are analogous to the parotid glands in mammals. These glands, situated in the temporal regions, are operated by the act of biting, when the gland is squeezed by the contraction of the temporal muscle, the venom being expelled in this fashion into the wound by means of the grooved or tubular fangs. (Fig. 170.) In the case of the African

"spitting cobras" the venom is ejected with great force into the face of the enemy.

The *venom*, a clear, amber-coloured fluid, is composed of modified proteins. It is of two kinds; that of the family *Viperidæ* (vipers) acts principally upon the vascular system, but that of the *Colubrinæ*, *Elapinæ* and *Hydrophinæ*, i.e. cobras and sea-snakes, acts upon the nervous system and brings about respiratory paralysis. The specific action of the venoms appears to depend upon the ferments and lysins they contain. As far as is known, the following substances enter into their composition, viz., fibrin ferments; proteolytic ferments; cytolysins acting upon red cells, leucocytes, epithelial and nerve cells, agglutinins, and neurotoxins with affinity for all nervous tissue, especially for the respiratory and vasomotor centres. It has been shown by Pepew that the addition of 0·4-per-cent. formol (10-per-cent. formaldehyde) to snake venom, and its maintenance at 38° C., transforms it into anavenin (analogous to anatoxin in diphtheria).

Several medicinal uses for snake venom have been suggested, and it appears from the work of Macfarlane and Burgess Barnett that the venom of Russell's viper acts as a certain styptic in hæmophilia. One drop of a 1 : 1000 solution of the venom, when added to ten drops of hæmophilic blood, causes clotting in seventeen seconds, although the blood itself took thirty-five minutes to clot. In a normal person hæmorrhage from a tooth-socket or tonsil-bed, and capillary oozing into an abdominal wound, are controlled at once. In hæmophilic patients with bleeding tooth-sockets, hæmorrhage ceases when the wound is lightly plugged with gauze soaked in venom 1 : 10,000. Cambrook has pointed out that, for dental purposes, the venom is unstable unless kept in an ice-chest. Cobra venom also possesses analgesic properties, and has been employed by Macht and others for the relief of pain, for which purpose the dried scales of the venom are dissolved in physiological saline and put up in glass ampoules. Usually two or three are first given to test whether the patient has an idiosyncrasy, and if not, full doses of 5 units are injected intramuscularly, and repeated daily if marked relief from pain is obtained. This venom has also been employed in the treatment of epilepsy, but the results are so far inconclusive.

Characters used for identification and classification.—Osteological and dental characters are employed to determine families and genera, and it is therefore necessary to understand the various types of ophidian skulls and the different arrangement of fangs and solid teeth. For generic and specific distinctions the form and number of the epidermal shields and scales are of great importance.

The arrangement of the scales on the head is shown in Fig. 171, and the arrangement of the prefrontal and preocular scales varies in different species and genera. In the crotalinæ, or pit vipers, there is a sensory uveal pit situated between the eye and the nostril.

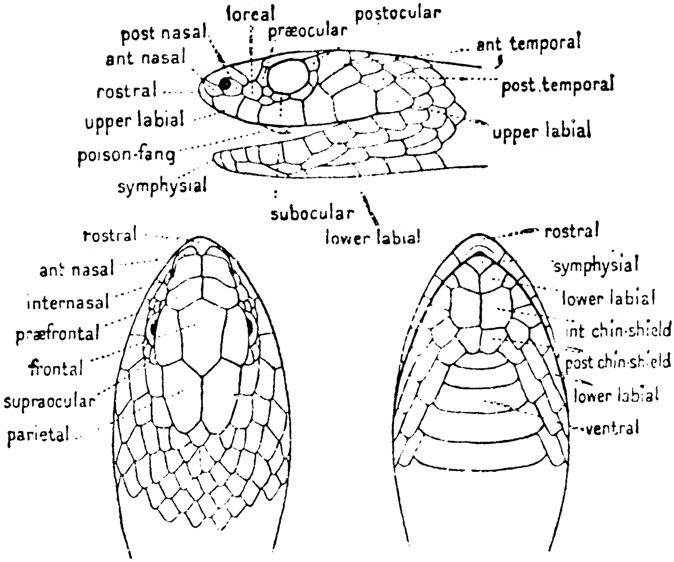


Fig. 171.—Head-shields of ***Causus rhombeatus.***
(*After Boulenger, "Proc. Zool. Soc."* 1915.)

Viperine snakes can generally be distinguished from the colubrinæ by their smaller size, the angular shape of the head, and the sharp stumpy tail. The maxillæ are vertically erectile, with enormously enlarged tubular fangs situated anteriorly (Fig. 172).

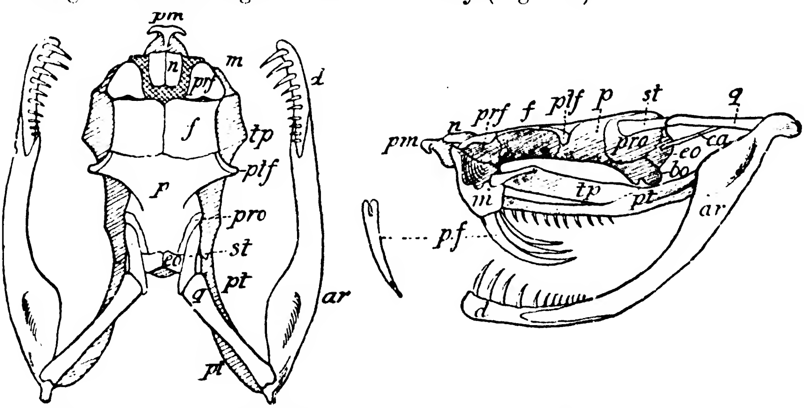


Fig. 172.—Skull of ***Trimcresurus gramineus,*** **upper view and side view.** (*After Boulenger, " A Vertebrate Fauna of the Malay Peninsula; Reptilia and Batrachia."*)

ar, Articular ; *bo*, basioccipital ; *ca*, columella auris ; *d*, dentary ; *eo*, exoccipital ; *f*, frontal ; *m*, maxillary ; *n*, nasal ; *p*, parietal ; *pf* poison-fang ; *pm*, præmaxillary ; *prf*, præfrontal ; *pro*, proötic ; *pt*, pterygoid ; *ptf* postfrontal ; *q*, quadrate *st*, supratemporal ; *tp*, trans-palatine.

In striking, the snake throws itself forward with great violence. On the whole the vipers strike with greater velocity than do the colubrids. Most strike with the jaws closed, but as the head approaches the victim, the mandibles are depressed by a rapid contraction of the digastric and other muscles and simultaneously the fangs are elevated and rotated forward. The fangs of the colubrids are grooved and are shorter than those of the vipers. Closure of the jaw is brought about by the simultaneous contraction of the temporal muscles which strongly elevate the mandible (Fig. 173). In vipers expulsion of the venom is instantaneous and independent of fixation of the lower jaw. Immediately following the insertion of the fangs and accompanying discharge of venom, contraction of the retractor muscles occurs,

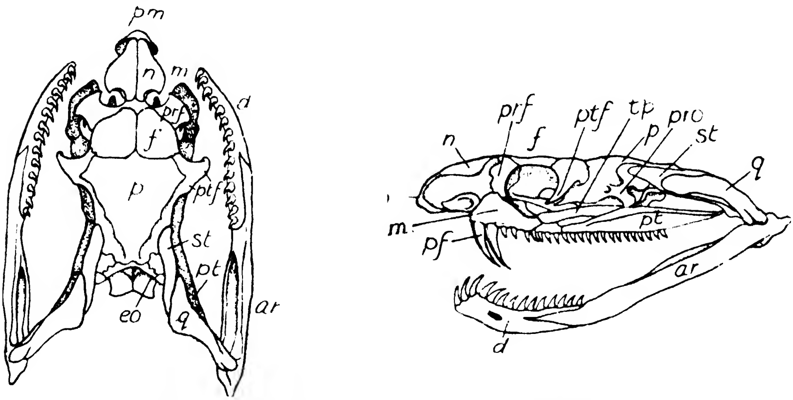


Fig. 173.—Skull of *Naja tripudians*, upper view and side view. (*After Boulenger, "Catalogue of Snakes,"* vol. iii.)

ar, Articular; *d*, dentary; *eo*, exoccipital; *f*, frontal; *m*, maxillary; *n*, nasal; *p*, parietal; *pf*, poison-fang; *pm*, præmaxillary; *prf*, præfrontal; *pro*, proötic; *pt*, pterygoid; *ptf*, postfrontal; *q*, quadrate; *st*, supratemporal; *tp*, transpalatine.

dragging the elevated fangs downwards and backwards through the tissues. Impression of the fangs and the pterygo-palatine indentations may be made in Kerr's impression compound of dental wax, and it has been found that the distance between the fang punctures affords a fair index to the venom-yield. Fatal results may follow inoculation from a single fang.

The lethal dose of venom varies within wide limits when tested on different species of animals. The killing capacity of different venoms for sheep, estimated in terms of average venom-yield, was found by Fairley to be: 118 for the Australian tiger snake (*Notechis scutatus*), 31·7 for the cobra, 2·2 for Russell's viper, 84·7 for the Australian death-adder (*Acanthopis antarticus*), 8·9 for the copper-head (*Denisonia superba*), and 1·5 for the black snake (*Pseudechis porphyracius*).

Symptoms of snake-bite in man.—The physiological action

and symptoms produced by snake venoms can be classified into two groups, the colubrine and the viperine.

1. *Colubrine.*—In the case of cobra-bite (Fig. 174) there is severe pain in the part, which soon becomes inflamed and œdematous. After an interval of an hour the patient becomes dull, apathetic, and unable to stand. Nausea and vomiting, with profuse salivation and paralysis of the tongue and larynx, supervene. Soon the respiratory centre becomes involved, and respiration ceases. Should the patient survive the paralytic symptoms, recovery is rapid. The pupil is contracted throughout.

The bite of the krait (*Bungarus fasciatus*, Fig. 175) is extremely dangerous, especially in Northern India; the symptoms are similar to those produced by the cobra.

The symptoms caused by the bite of the Australian colubrines

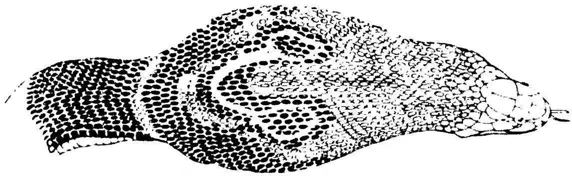


Fig. 174.—The cobra (*Naja tripudians*).

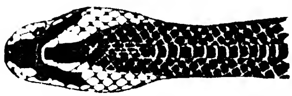


Fig. 175.—The krait (*Bungarus fasciatus*).

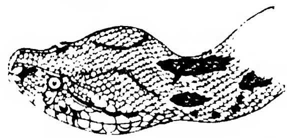


Fig. 176.—The daboia (*Vipera russelli*).

may not be very severe, but the constitutional effects appear with great rapidity—sometimes in as short a period as fifteen minutes. A feeling of faintness and an irresistible desire to sleep are soon followed by paresis of both legs, vomiting, and cardiac paralysis. The pupil is widely dilated and insensible to light. Should the patient survive the coma, recovery is complete and no sequelæ occur.

2. *Viperine.*—As the type of lesion produced by the viperines, that of Russell's viper (*Vipera russelli*, Fig. 176) may be described. This species is extremely deadly; the bite causes severe pain with rapidly forming and extensive œdema, together with blood-stained discharge, and ecchymoses around the site of the punctures. Collapse, small thready pulse, nausea and vomiting, and dilated pupils, insensitive to light, soon supervene, together with a loss of consciousness more or less complete, from which a temporary recovery sometimes occurs. Should the effects of the now diffused toxin wear off, the local condition of the wound becomes aggravated; extensive local suppuration and sloughing, malignant œdema, or even tetanus and hæmorrhages from

the mucous surfaces—hæmaturia or melæna—may occur. There is no paralysis of the muscles, but Rogers has shown that the viperine toxin produces a vasomotor paralysis. It is more easily destroyed by caustic agents than colubrine venom.

The bite of *Echis carinatus* (Fig. 177) is less dangerous than that of the daboia, but is in many ways similar in its effects.

The bites of the rattlesnakes—*Trimeresurus* and *Crotalus* (Figs. 178, 179)—are remarkable for the local disturbance they produce. Constitutional paralytic symptoms come on quickly, usually in less than fifteen minutes. Should the patient recover from this state, the swelling and discoloration extend up the limb and trunk, and general symptoms of blood-poisoning with pyrexia, restlessness, and delirium set in. The wound itself suppurates freely and may become hæmorrhagic, or even gangrenous. The symptoms produced by the

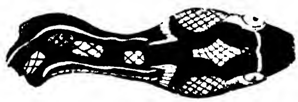


Fig. 177.—The phoosa (*Echis carinatus*).

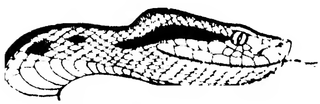


Fig. 178.—*Trimeresurus lanceolatus.*

Fig. 179.—Rattlesnake (*Crotalus terrificus*).

bite of the European vipers resemble those of *Crotalus*, but are much milder.

The mortality from snake-bite, even of the most venomous varieties, is not so great as is popularly supposed, and is estimated at about 30 per cent. That it should not be more is probably due to the fact that, unlike what takes place in experimental animals, the reptile is seldom able to inject a full dose of venom. If given a fair chance, the cobra is able to inject no less than the equivalent of twenty lethal doses at a time.

Treatment.—To be effective, all treatment should be vigorously and promptly applied. It should be directed, firstly, to prevent absorption of the poison; secondly, to neutralize, as far as possible, its toxic effects. A ligature should be tied around the limb, immediately above the bite; for this purpose, if it is at hand, a stout india-rubber band, firmly applied, is the best ligature, or strips of clothing may be loosely knotted round the limb and subsequently tightened by twisting with a stick. It has been shown that by *local venesection* one-half to one-third of the injection venom can be removed. A

second ligature, tight enough to obstruct the return of the venom, but not the arterial circulation, is applied immediately distal to the arterial ligature. An incision is made into one of the veins draining the bitten area, and a series of blood-lettings carried out by loosening the arterial ligature whilst leaving the venous one in position. In the case of the colubrines, this probably has little or no effect in preventing the absorption of the neurotoxins, but in the case of the viperines it is no doubt very effective in so far that it localizes the fibrin ferments, causes extensive intravascular clotting in the bitten part, prevents the process from becoming generalized, and affords time for the action of remedies.

Amputation of the part above the bite has been proved to be effective, if performed *immediately*.

The absorption time of lethal doses of snake venom has been determined by experiment. Acton and Knowles injected 100 mg. of cobra venom into the tips of the tails of four dogs and amputated them 7·5 c.m. above the site of inoculation at one-minute intervals. All the animals died within a period of 45–85 minutes. Later, Fairley found that, in sheep bitten over the metacarpal bone by tiger snakes, ligature and excision saved life only if applied within two minutes.

The next steps must be directed towards destroying the poisons remaining at the site of injection. This is best effected by freely incising the bite in the direction of the lymphatic and venous circulation. The wound should then be well swabbed out with a strong solution of potassium permanganate; this destroys any toxin with which it comes in contact. Some advocate the rubbing-in of crystals of the same substance. Acton and Knowles have advocated the injection of 10–20 c.c. of a 5-per-cent. solution of gold chloride in ox-bile as being an improvement upon potassium permanganate, and recently have stated that dichloride of platinum (1 : 2000) is even better. Unfortunately, both these substances cause necrosis of the tissues.

Contrary to the popular idea, sucking the wound is useless.

Alcohol and strychnine were formerly regarded by some as antidotes, but are now known to have no efficacy whatsoever.

Serum treatment.—It has long been known that immunity could be produced in animals by repeated and progressive inoculation of venom; a similar result is produced in men who have been repeatedly bitten by snakes of one species. This immunity, however, is specific only for the venom of the particular species. Calmette attempted to produce, in *antivenene*, a serum which should be active against all snake venoms, but his claim to have done so has not been substantiated.

The serum prepared against cobra venom is found to be antitoxic to the homologous venom, and to a certain extent to that of *Bungarus fasciatus*, but is without action on the viperine venoms of daboia, *Echis*, *Trimeresurus*, and *Crotalus*. The serum produced against

daboia venom has no action whatever upon the venoms of *Naja, Bungarus*, etc. On the other hand, it has been shown that the hæmolytic properties of Indian and African cobra venoms are practically identical, and the antivenene prepared in India against *Naja naia* is equally serviceable against *N. flava*, that prepared in South Africa against *N. flava* acting similarly against *N. naia*.

In practice one is met with the very important drawback to the use of an antiserum that, though specific towards some other species of snakes, it may be impotent as regards the particular species concerned. The only practical method of meeting this unfortunate circumstance is to issue an antiserum effective against the most common and the most dangerous snakes in any given country. All antivenenes are relatively weak in their action as compared to antidiphtheritic and antitetanic serums. The antivenene should be injected intravenously in large amounts and as soon after the bite as possible. Acton and Knowles have demonstrated that such a serum must be given before the minimum lethal dose of venom has been absorbed, and that it requires no less than ten minutes to find its way into the circulation. The injection should be done *intravenously*, and at least 100 c.c. should be given. In India the serum treatment, if available, should be employed in every case, on the chance that the snake was either a cobra or a daboia. The longer the antivenene is withheld, the greater is the dose required to save the animal. The early application of the tourniquet, by its localizing influence, enables the effective dose of serum to be reduced by one-half to one-third.

There is still much work to be done before an efficient polyvalent serum can be produced. One of the difficulties encountered is that every injection of venom into the horse for the production of immunity gives rise to abscess-formation, and that the whole process of preparation lasts from a year to a year and a half. It is estimated that in Brazil the death-rate from snake-bite has, by prompt antivenene treatment, been reduced from 25 per cent. to 2·5 per cent.

Other measures.—Little else can be done, except to keep the patient warm. Small doses of alcohol, ammonia, and strychnine should be given as stimulants, but the practice of exhibiting almost poisonous doses of alcohol cannot be too strongly deprecated. Rogers has advocated, on physiological grounds, the employment of adrenalin in those snake-bites in which the toxins have a marked paralytic action upon the vasomotor centres. Acton and Knowles advocated artificial respiration in colubrine poisoning.

Venomous Lizards

All lizards are absolutely non-poisonous, with the exception of a single genus, easily recognized, inhabiting Mexico and Arizona. This genus, *Heloderma*, consists of two species, *suspectum* and *horridum*, both heavy, stout lizards, yellow or shrimp-pink in colour, with black bead-like scales. They are desert-dwellers, and store fat in their swollen tails to tide them

over periods of famine. They are popularly known as the "Gila[1] monsters," because they were first discovered near the village of Gila.

The poison apparatus is in the lower jaw, where venom-secreting submaxillary glands are connected by ducts with grooved teeth. The symptoms of poisoning start with paralysis. A large dose produces dyspnœa and convulsions. Post-mortems on animals show a greatly dilated heart and venous congestion in the internal organs. Changes in the spinal-cord ganglion cells have also been observed.

Poisonous Fishes

Poisonous fishes exist in most tropical waters, especially among the coral reefs of the Pacific and Indian Oceans. Their venom may be conveyed to man either through their bite or by means of stings. In the one case the poison is secreted by certain epithelial glands within the mouth; in the other, by poison-glands connected with barbs in the dorsal fin. The former class comprises more than one hundred species of the genus *Murœna*, all of which possess powerful teeth capable of inflicting bites (Fig. 180). The poison secreted by the glands courses down the hollow teeth. The

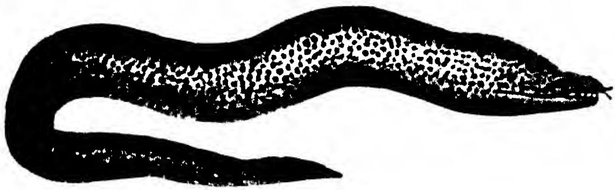


Fig. 180. *Murœna moringa*. (*After Calmette.*)

effect of the venom on man is neuro-cardiac. The other class contains a great number of widely separated genera. In some, the poison finds its way to the exterior only when the barbs are broken, and produces severe inflammation in the wound and, it may be, tetanic symptoms. *Synanceia*, a spinous species, is widely distributed throughout the Indian and Pacific Oceans, and is one of the Scorpænidæ (scorpion fish); *S. verrucosa* is the most toxic. The poison apparatus is connected with the dorsal fin. *Plotosus anguillaris*, known as "machoira" in Mauritius, has a similarly wide distribution; while *Saccobranchus fossilis*, in the waters of India and Ceylon, produces similar symptoms.

In South American waters, several species of *Thalassophryne* have dorsal spines containing a central poison-duct connecting with the glands. Species of *Trachinus* found in northern waters, as well as in the Mediterranean, have two sets of poison barbs, on the operculum as well as on the dorsal fin. The venom has a general action on the heart, besides the purely local effect.

Many species of *Scorpœna*, over forty in all, are found in tropical waters; their integument is provided with numerous rays, the stings of which may excite convulsions and even cause death.

Poisonous Shellfish

In the South Pacific Islands fatal cases of poisoning may be due to bites of certain shellfish of the genus Conus, all of which are adorned with brightly-coloured shells. Five at least are known: *Conus tulipa*, *C. marmoreus*,

[1] Pronounced "heela."

C. geographus, *C. textilis*, and *C. aulicus*. They are provided with a long tubular proboscis which can be protruded beyond the shell, and opening into it is a sac containing two rows of hollow teeth. The symptoms are acute pain, swelling, numbness, and spreading paralysis. There may be early drowsiness, deepening into coma and death. When bitten in this manner, the Polynesians make small incisions round the bite to cause blood to flow freely. Flecker (1936) has recorded a fatal case in a European, on Haymen Island, North Queensland.

Poisonous Sea-anemones

Sea-anemones of the genus *Hellenopolypus* and *Aktinion* give rise to sponge-fishers' or "Skevos-Zervos" disease. This is effected by contact, itching and vesication, pustulation, nausea and vomiting being set up. The toxin acts like cantharides, and the lesions are due to urticating cells in the tentacles. Washing with vinegar and the application of olive oil is the best treatment.

Jelly-fish Poisoning

Medusæ of the genus *Obelia* contain in their ectoderm numerous clear ovoid bodies, the stinging capsules or *nematocysts*, which serve as weapons of offence. The whole apparatus is developed in an interstitial cell (cnidoblast) which, as it approaches maturity, migrates towards the surface and at one point is elongated by a delicate process—the cnidocil or trigger hair. When this is touched the cnidoblast undergoes a sudden contraction and causes an eversion of the thread, at the base of which are minute barbs which are poisonous and produce a numbing effect. In human beings the stings produce a painful local swelling and a disagreeable urticaria, and, in susceptible individuals, shock and collapse.

The Portuguese man-of-war (*Physalia*) is provided with a characteristic stinging apparatus. From the underside of the float there hang filamentous tentacles (gastrozooids, dactylozooids and branching blastostyles), some of which are long and retractile and contain batteries of stinging capsules which produce severe dermatitis and irritation in the skin of human beings who come into contact with them.

POISONING FROM THE INGESTION OF POISONOUS FISHES

Cases of fish-poisoning arising from the eating of flesh of fishes containing some intrinsic toxin occur more commonly in the tropics than in more civilized countries. In many instances these fish may be eaten with safety except at certain seasons of the year; in others the poisonous qualities are acquired only after feeding or living in certain localities.

The barracouta (*Sphyræna barracuda*) is eaten widely throughout the South Atlantic; it is the large fishes, especially those that are spawning, which are apt to be poisonous, and the symptoms are mainly gastro-intestinal.

In these waters Cigatuera poisoning results from eating *Sphyræna picuda*; within a few hours of ingestion, abdominal pain, diarrhœa, and vomiting ensue.

There are various sprats (*Clupidæ*) in tropical waters which are apt to acquire poisonous properties; among them is *C. longiceps*, a sardine found in Ceylon waters, which occasionally may produce collapse and even death.

Many species of the widespread genus *Tetrodon* are poisonous, such as the "death-fish" of Hawaii—*T. hispidus*—while other species occur in Japanese and Korean waters. The poison is contained in the ovaries and

in the eggs, and causes gastro-intestinal and nervous symptoms, sometimes culminating in syncope or coma.

The flesh of certain large fishes normally constituting excellent food, such as the king-fish (*Scomberomorus cavalla*), may occasionally exhibit toxic properties.

In all forms of fish-poisoning the most effective *treatment* is to evacuate the poison by washing out the stomach and administering purgatives. Other symptoms must be treated on general lines with stimulants, hot-water bottles, etc., and injections of morphia, if necessary, to alleviate the pain.

Scorpions and Spiders (Arachnida)

Scorpions are very common in the tropics, and their stings are very painful and cause a considerable amount of inconvenience, though they are not exactly dangerous, except to young children, in whom, in addition to local

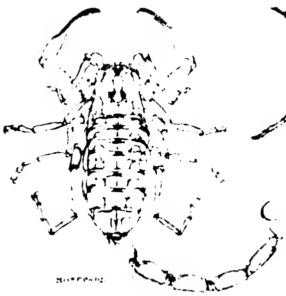


Fig. 181. Scorpion (*Buthus* sp.). Half nat. size.

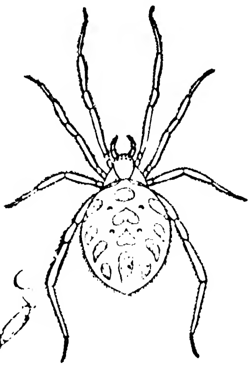


Fig. 182.—*Latrodectus 13-guttatus*. × 2. (*After Hirst, "Journ. Economic Biol."*)

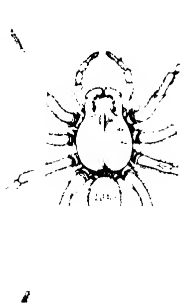


Fig. 183.—*Lycosa tarentula* Half nat. size.

symptoms, muscular cramps, profuse perspiration, pyrexia, vomiting, and convulsions may be produced. Deaths have been reported from North and South Africa, the West Indies, Mexico, Korea, and Manchuria. In Trinidad, glycosuria, hyperglycæmia, pancreatitis, and even pancreatic cysts are described as sequelæ to scorpion stings.

In Southern Europe and North Africa the black scorpions, *Euscorpius italicus* and *Buthus maurus*, in Mexico a species known as the "durango" (*Centrurus*), in Brazil *Tityus serrulatus*, in Manchuria *Buthus martensi*, are specially dreaded (Fig. 181).

The paired poison-glands are situated in the last or postanal segment of the tail, which is jointed and very flexible, so that it can be curved forwards over the body when the scorpion is striking. The venom which it ejects is in many respects like that of the cobra, but far less toxic.

In the *treatment* of scorpion-sting in children, it may be necessary to incise and thoroughly wash out the sting with a strong solution of potassium permanganate. In adults, pain is the predominating symptom, and this, according to Tomb, can be immediately relieved by a drop of liquor ammoniæ

fortis, which can be applied with the stopper of a bottle. A more liberal application of diluted ammonia is also effective, but not so immediate in action. Dyce Sharp, from experiences mostly in his own person, warmly advocates immediate injection of an ampoule of novocain and adrenalin in the vicinity of the sting. For the severe intoxications of children Todd produced an efficient antitoxin. The venom extracted from the dried stings and venom-glands by means of normal saline is toxic to the horse, goat, and most laboratory animals; while the desert fauna, such as the desert rat, the jerboa, the fennec fox, and the hedgehog are immune. The antitoxin has been prepared from horses by subcutaneous injection of graduated doses of venom. In doses of 5 c.c. it exerts both a prophylactic and a curative action.

Spiders.—Nearly all spiders (*Araneæ*) possess poison-glands, the venom of which is injurious to insects, but only a few species are dangerous to man. Certain species of the genus *Latrodectes* are believed to be very poisonous. In New Zealand one species, *L. hasselti*, known as the "katipo," in Southern Europe *L. tredecimguttatus*, the "malmignatte" (Fig. 182), and in North and South America *L. mactans*, *L. curacaviensis*, and *L. geometricus* occur.

L. mactans is known in California as the "Black widow spider"; the adult female is glossy black with crimson hourglass markings on the abdomen. In Turkestan *L. tredecim-guttatus* is known as the "Karakurt spider"; in Australia, *Atrax robustus* as the "Funnelweb spider" and in South Africa *L. indistinctus* the bite of which is much feared, as the "Kroppie spider."

The toxin of the poison-glands has been shown to be a powerful hæmolysin, causing inflammation and œdema at the site of the injection, together with numbness of the part and, it may be, an urticarial rash. Most observers describe intense nerve-pain, which is said to be due to stimulation of the myo-neural junctions by the venom. A rigidity and spasm of most of the muscles supervenes, especially those of the abdomen, which becomes "board-like," bringing about a resemblance to appendicitis. Sloughing of the skin in the neighbourhood of the bite may occur. *Treatment* consists in washing out the wound with a solution of potassium permanganate (1 : 4000), and administering the drug in doses of one teaspoonful every two hours.

Intravenous injections of calcium gluconate (10 c.c. of a 10-per-cent. solution) are said to relieve the pain and decrease the muscular spasm. In South Africa a serum which neutralizes the venom of *L. indistinctus* has been prepared by Finlayson. Similar sera have been used in the Argentine and Russia against the local species of *Latrodectes*.

In Peru a pruning spider, *Glyptocranium gasteracanthoides*, which lives in the leaves of vines, and is identified by its ash-grey colour and large globular abdomen with two prominent tubercles, produces, according to Escomel, the same symptoms as *Latrodectes*, and sometimes hæmaturia.

The true "tarantula" spider, *Lycosa tarentula* (Fig. 183), occurs in Southern Europe. Mysterious properties have been attributed to its bite; apparently in some specially susceptible people œdema of the eyelids and pyrexia are apt to result, and its bite gives rise to the hysterical disease known in the Middle Ages as "tarantism." The so-called tarantulas of tropical countries are bird-eating spiders belonging to the family Mygale. They are trap-door spiders, terrestrial in their habits, with prominent projecting mandibles which give them a terrifying appearance. The North African species, *Chætopelma olivacea*, is much feared by the Arabs, and its bite is said to give rise to acute inflammation.

CENTIPEDES (MYRIAPODA)

The Chilopoda, to which the poisonous genus *Scolopendra* belongs, are widely distributed in the tropics. They are large species, and possess a poison apparatus at the base of the first pair of appendages, which are modified so as to form jaws. The tropical species, *Scolopendra morsitans*, reaches a large size, up to 6 in.; the venom causes both local and general symptoms. The site of the bite becomes inflamed and the starting-point of a lymphangitis; dizziness, headache, and vomiting may ensue. *Treatment* consists in bathing the part with a strong solution of ammonia, 1 : 5 or 1 : 10. It may be necessary to give hypodermic injections of morphia to allay the pain.

CHAPTER XLVII

MYIASIS AND LEECH INFECTION

UNDER the term " myiasis " it is customary to include a number of traumatic conditions of the tissues caused by partial parasitism by the larvæ of certain *muscoid* flies.

Some of these flies deposit their eggs or larvæ in wounds or in the natural openings of the body; in other cases the grubs, on hatching, burrow into the subcutaneous tissues: others imitate the habits of a tick, and emerge from their hiding-places to feed on the blood of man by puncturing the skin. Intestinal myiasis appears to be an accidental condition in which the larvæ pass through the intestinal canal.

NASAL, AURAL, AND OCULAR MYIASIS

The screw-worm fly, *Cochliomyia hominovorax* (Syn., *Chrysomyia macellaria*) (Appendix, p. 1009), is a common insect in America, ranging from Canada to Patagonia. It is most active during the heat of the day, and normally deposits its eggs upon open wounds or on dead animals. It attacks people sleeping in the open air, especially those who have offensive discharges which attract it.

Comparatively frequently the fly lays its eggs in the nasal and aural cavities, as well as on open sores. The larvæ, known as screw-worms, burrow into the tissues, devouring in their passage mucous membrane, muscle, cartilage, periosteum, and even bone. They may penetrate the brain and cause death.

Chrysomyia bezziana (Appendix, p. 1009), is a true myiasis-producing fly; it never breeds in dead, but always in living tissues. It has a wide distribution, being found in India and Cochin-China. It appears to have a predilection for human beings in India, the female, as in *Cochliomyia macellaria*, laying her numerous eggs in the nasal cavity or in tissues from which an offensive discharge emanates.

Rhinœstrus purpureus (Œstridæ).—The larvæ of this species are parasitic in the nasal passages of equines in Southern Europe, Asia Minor, and Africa, but occasionally the fly attacks man, depositings its eggs in or near the eye, where the larvæ may be seen, shortly after hatching, moving beneath the conjunctiva, and may lead to the loss of this organ. (*See* Appendix, p. 1009.)

Wolfahrtia magnifica (Appendix, p. 1006) belongs to the family Sarcophagidæ, or flesh flies; it is the only specific myiasis-producing fly found in man in Europe; it has a wide distribution in Asia Minor and Egypt. In habits it is similar to the species previously described.

Ocular myiasis (ophthalmomyiasis).—In tropical and subtropical countries the larvæ of flies may be deposited on the lids and in the conjunctival sac, whence they may pass into the lachrimal passage, penetrate the conjunctiva and sometimes the sclera, and so gain entrance to the intra-ocular

tissues. The parasites so far recorded are *Rhinœstrus bovis*, *Hypoderma bovis*, *H. lineata*, *Sarcophaga*, *Gastrophilus intestinalis* and *G. equi*. McBride has recorded a case of conjunctivitis due to larvæ of the bot-fly (*Œstrus ovis*) in the conjunctival sac.

Subcutaneous Myiasis

In South America the "macaw-worm" or "Ver macaque" (p. 1012) (*Dermatobia cyaniventris*), infests cattle, indigenous mammals, and also man.

The eggs are deposited on the skin or clothes of human beings, and do not hatch for a day or two. When hatched, the larvæ penetrate the skin

Fig. 184.—Lesions on back caused by *Cordylobia anthropophaga*. (*Orig.*)

and produce an inflammatory tumour, from the aperture of which there exudes a seropurulent fluid containing their black fæces. They have been reported from various regions of the body, and their presence is usually accompanied by great pain, especially when they are actively moving. Busck reports that before they reach maturity the larval skin may be shed and exude from the opening in the skin of the host. In removing them there is apparently no need to use a knife, for the aperture of exit may be widened by stretching with forceps, and the larva then slips out, aided by properly applied pressure, for its narrow end is situated towards the opening in the skin.

In tropical Africa, the tumbu fly, or ver du cayor (*Cordylobia anthropophaga*, p. 1010), produces much the same results. According to Roubaud, Blacklock, and Thompson, the eggs are first deposited on the ground, and the active young maggot attacks and penetrates the skin of its host, especially on the forearm, scrotum, upper part of the thigh, and buttock. The lesion resembles an inflamed tumour, from which the larva emerges in six or seven days. In the ordinary course of events these tumours do not suppurate. (Fig. 184.) The fly usually attacks other mammals besides man.

The Treatment of Septic Wounds by Fly Larvæ

Baer, having noticed the effect of accidental larval infestation of wounds during the Great War, treated 89 cases of osteo-myelitis with larvæ of blow-flies (*Phormia regina*, *Lucilia sericata* and *L. cæsar*) and considered that they cleared the wounds of dead tissue by their digestive action through the excretion of tryptase, inhibited the growth of pathogenic bacteria by rendering the wounds alkaline, and possibly produced other biochemical effects. In the Sudan, Grantham-Hill has found the larvæ of *Wolfahrtia nuba* to be the most common and most effective. Wounds to be treated were thrown open as freely as possible by free incision of soft tissues and canalization of bone, where necessary, being packed with sterile liquid paraffin for forty-eight to

Fig. 185.—Larva migrans. Infected at Durban, April 20, 1921 : first symptoms noted July 22, 1921. (*Orig. case.*)

seventy-two hours before treatment with larvæ. After removal of the packing and drying of the cavity, from 30–200 larvæ were introduced directly from sterile test-tubes with a flat probe.

There is usually an immediate flooding of the wound with serous exudate which has to be swabbed out ; the skin edges are then painted with collodion, and sterilized fine wire gauze fixed over it with adhesive strapping. After 48 hours the larvæ are found to be fully grown and, if left beyond that period, endeavour to escape in order to pupate. Small sequestra of bone are freed and consumed by the larvæ.

Larva Migrans

Synonyms.—Myiasis Linearis ; Creeping Eruption ; Dermatitis Linearis Migrans.

This condition (Fig. 185), first described by Lee in 1874, and at a later period by Crocker, is said to be common in Russia and, according to Kirby-Smith, extremely frequent in Florida. Certainly it is not infrequent in the

tropics, especially in Ceylon and South Africa. Here multiple lesions on the legs and feet are produced by the burrowing under the skin of a larval nematode, which has now been shown by Kirby-Smith to be that of *Ancylostoma braziliense*, the common ancylostome parasite of cats and dogs in that region. These observations were confirmed by Fülleborn, who has shown that similar lesions may be artificially produced in volunteers by the larvæ of *Uncinaria stenocephala*, and to some extent, also by *Ancylostoma caninum*. Shelmire and Heydon, and also Fülleborn in experiments on his own hands, have shown that the œdema and irritation are considerable.

In South Africa, especially in Natal and Zululand, where "creeping eruption" or "sand-worm," as it is called, is very common, Murray (1939) has now, by aid of cedarwood-oil technique, proved that the burrows are produced by a mite, possibly related to *Tetranychus molestissimus*, which is found in Argentine and Uruguay and attacks man and animals. The tracks in the skin are 0·33 mm. in diameter. The mite, and sometimes also its eggs, is easily demonstrated at the end of the burrow. A drop of distilled water on a clean slide prepared with Mayer's egg albumin facilitates the procedure.

In Florida the disease has a definite seasonal prevalence during the summer months, following periods of rainy weather. Most of the cases originate on the beach above high water mark. There is some evidence that it is connected with sewage disposal. Dogs and cats are the hosts of the adult worm.

It is possible, as Fülleborn and da Rocha-Lima suggest, that the tropical form differs from that described in Russia and America. The former appears to be due to the burrowing of a fly larva under the epidermis. These larvæ have been identified as being *Hypoderma*, *Gastrophilus hæmorrhoidalis*, and *G. veterinus*. The lesions of the ancylostome larvæ group can be distinguished from those of *Gastrophilus* by being much shorter and more complex.

Children are mostly attacked between the fingers and toes.

Unlike the itch-mite, it burrows on indefinitely, like a mole, and forms a red line or narrow raised ridge ⅛ in. broad. The parasite appears to travel at the rate of ½–1 in. in twenty-four hours. The line zig-zags and twists about, but does not bifurcate, and may be found in any part of the body—the face, chest, or more particularly the soles of the feet and the legs. While the advancing end of the line progresses, the opposite end fades away. The only subjective symptom is itching (Fig. 186). The disease may be of very long duration, and is accompanied by intense itching; sometimes bullæ are formed.

Austmann has used Lombard's method of clearing the living skin to demonstrate the larvæ of *Gastrophilus* in cases produced by this insect. Ordinary machine-oil is used and the epidermis cleared around the line of creep. Using the binocular dissecting microscope the parasite may be seen lying between the cornified and granular layers of the epidermis. With a magnification of 150 diameters, details of structure can be clearly seen.

Treatment by injection of cocaine and parasiticidal substances in advance of the migrating larva has so far proved to be unsatisfactory. Excision of the portion of the burrow containing the advancing larva should be attempted. Ethyl acetate, applied on cotton or gauze or used in a flexile collodion, is effective in many cases. Refrigeration with ethyl chloride has been found to be most effective. An area of one and a half inches at the visible end of the burrow should be frozen for two to four minutes. If there are multiple burrows, the ethyl chloride should only be applied to a few at a time. Carbon-

dioxide snow is very painful, and the blisters thus produced heal very slowly. There is often a secondary dermatitis which must be treated as well. Rubbing oil of chenopodium into small incisions in the skin in front of the advancing larva has also been found efficacious. For the irritation, *heliobrom* (Teichgräber) in 10-per-cent. alcoholic solution is most useful.

Blood-sucking Larvæ

Auchmeromyia luteola (Appendix, p. 1006), the larva of which is commonly known throughout the Congo as the "floor maggot," has a wide distribution throughout tropical Africa, from Northern Nigeria to Natal. The adult fly is usually found among the thatch and beams of the walls and roofs of

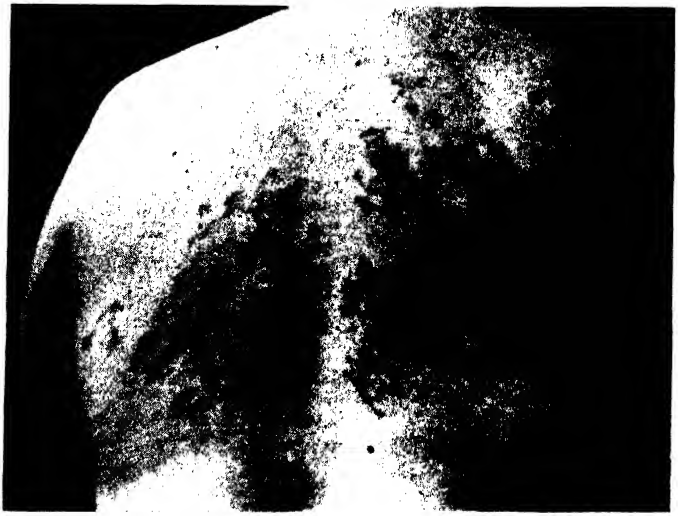


Fig. 186.—Multiple burrows of larva migrans, from the Gold Coast. (*Orig.*)

native huts, and deposits its eggs in crevices of the mud floors. Here the larvæ hatch and move about in the moist earth. They emerge from their hiding-places and feed mainly at night.

The sucking of blood is effected in a curious manner: the head segment is retracted, and the lips of the second form a sucking disc attaching the larva to the skin of the host; the skin is scarified by the curved hooks, and thus blood is drawn. The larva itself soon assumes a red colour due to the absorbed blood. It is said that the bite is not irritating.

The larvæ of *Cordylobia anthropophaga* (*vel. grünbergi*) (*see* p. 1010) and *Dermatobia cyaniventris* (*see* p. 1012) burrow under the skin and form subcutaneous abscesses. In the case of the former a remarkable example of metazoan immunity has been found to be produced by Blacklock and Gordon (*see* p. 1010).

Intestinal Myiasis

Residence in the alimentary canal of some vertebrate animal is a regular feature in the life-history of many dipterous insects. The eggs of the insect

are either licked from the skin or swallowed in the food on which they had been deposited. In this way they are transferred to the stomach, where, after a time, the larvæ are hatched out and undergo development. In due course they appear in the fæces. Man is not infrequently victimized in this way, especially in tropical countries. Sometimes, until a correct diagnosis is arrived at, not a little alarm is caused by the appearance of these creatures in the stools or vomit. They are easily recognized. The ringed, cylindrical body, $\frac{1}{2}$–1 in. in length according to species, broad at one end, tapering at the other, and usually beset with little spines or hairs, is sufficiently diagnostic (Fig. 187.)

Already we know over twenty species of diptera whose larvæ have been found in or expelled from the human intestinal canal.

In Europe the majority of cases of intestinal myiasis, a not infrequent occurrence, are caused by *Fannia canicularis* (a fly closely resembling the common housefly, and erroneously considered a young form of the latter on account of its smaller size) and the closely related *F. scalaris*. Occasionally pains in the abdomen, vomiting, and diarrhœa may ensue, and there may be

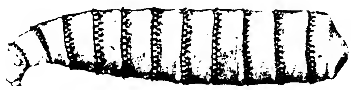


Fig. 187.—Larva of *Calliphora vomitoria*.

evidences of toxic absorption ; more usually these occur where the ingested larvæ are those of the cheese maggot, *Piophila casei*. Larvæ of the common house-fly (*Musca domestica*) have been found in numbers in the stomach in the Philippines. In Africa the insect commonly found is *Chrysomyia chloropyga*, and occasionally *C. putoria*.

A dose of castor oil will probably suffice to expel any of these creatures that may not have been passed spontaneously.

A rational prophylaxis would consist in the covering up of food after it has been cooked, in order to prevent the access of flies.

Instances in which the larvæ have been discharged per urethram have also been met with, though more rarely.

Leech Infection

In the grass and jungle lands of many tropical and subtropical countries land-leeches, probably of special species, often occur in great abundance ; so much so that in some circumstances they may prove to be something more than a nuisance. *Hæmadipsa zeylanica* is one of the most active, as well as best known, of these. Before feeding, when outstretched, it is about an inch in length and about the thickness of a knitting-needle. It clings to a leaf or twig, awaiting the passing of some animal, on to which it springs with remarkable activity. It at once attaches itself to the skin and proceeds to make a meal on the blood. Animals are sometimes killed in this way ; men even have been known to succumb to repeated small bleedings by these pests. It is necessary, therefore, when passing through jungle lands

in which leeches abound, to have the feet and legs carefully protected. The bite is not infrequently the starting-point of a troublesome sore.

In the south of Europe and in the north of Africa the horse-leech, *Limnatis nilotica* (Fig. 188), sometimes gets into the gullet and nostrils of men as well as of animals. It has occasionally caused death by entering and occluding the air-passages. These leeches are a source of inconvenience to French troops in Algeria, and are mentioned as occurring in Napoleon's army in its retreat through the Sinai Peninsula; and several cases were noted among British troops during the late Egyptian and Palestine campaigns. In Formosa, Manson heard of and saw several instances of a similar form of parasitism

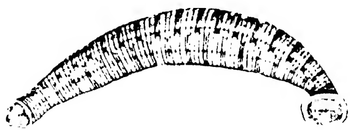


Fig. 188.—*Limnatis nilotica.* Half nat. size. (*Sheppard, del.*)

both in men and in monkeys. To what particular species the leech in these cases belonged is not known. Doubtless, when very young the leeches were taken in unperceived with foul drinking-water, and, wandering round the soft palate, found their way into the nose. Occasionally, in the cases referred to, the creatures would protrude from the nares and wander over the upper lip. For a long time they contrived to elude all attempts at capture. By dipping the face in cold water they can generally be persuaded to show themselves. In one instance the leech dropped out spontaneously. In another—an American naturalist who had been travelling much in the interior of Formosa, and who had suffered from severe headache and profound anæmia, the results of repeated epistaxis—Manson succeeded in removing the leech by attaching through a speculum a spring forceps to its hinder end, and afterwards injecting salt and water. It would be well to bear in mind that in tropical countries persistent headache, associated with recurring epistaxis, may be caused by a leech in the nostril.

APPENDIX

Section A.—Medical Zoology

I. MEDICAL PROTOZOOLOGY

The distinguishing characters of the commoner intestinal protozoa, as seen in fresh preparations of fæces and when stained by Weigert's iodine, are shown in Plates XXIX and XXX

INTESTINAL AMŒBÆ

Entamœba histolytica (Schaudinn, 1903) (syn. *Endamœba dysenteriæ*) (Fig. 189), the pathogenic amœba of man, has been considered in some detail above (p. 524), but a short summary may be given here. These amœbæ vary very much in size; as a rule they measure 20–30 μ in diameter and when active they eject characteristic hyaline pseudopodia. The movements are ribbon-like, and these masses of protoplasm glide across the stage like a "slug moving at express speed." The cytoplasm is divisible into two zones—an outer clear ectoplasm and a granular endoplasm. The nucleus, which is generally invisible in the living state, has a characteristic structure with small central karyosome, as is shown in the accompanying figure (Fig. 189, *1*). Vacuoles are not present in healthy living individuals, though they may appear in the protoplasm immediately before death. The large active entamœbæ, known as the vegetative forms, live in the intestinal wall at the bases of the lesions they give rise to, and there undergo binary fission. They ingest red blood-corpuscles, leucocytes, and other portions of the tissues in which they live; this habit serves as a distinguishing feature between *E. histolytica* and the non-pathogenic amœbæ. On cessation of a vegetative life they pass on to encystment, first becoming precystic forms.

The *precystic* forms of *E. histolytica* are probably developed from larger amœbæ by fission and, by frequent division, small daughter-amœbæ are produced. A shortage of food probably provides the stimulus which leads to encystment. Precystic amœbæ are sluggish and their cytoplasm is devoid of food vacuoles. On account of their small size they were formerly known as *E. minuta*, and according to the particular race they may vary in size from 5 to 20 μ.

Cysts.—According to Wenyon and O'Connor, Dobell and Jepps, there are different races of *E. histolytica*, distinguishable by the size of their cysts (Fig. 189, *2-5*). The smallest measure 7–9 μ or less in average diameter, the largest about 15–20 μ The mature cyst is quadrinucleate, and very commonly contains within its cytoplasm refractile *chromatoid bodies*; a *glycogen* mass is also usually present and becomes brown in colour upon the addition of iodine solution. The nuclei within the cyst retain the characters of those of the vegetative form.

According to Yorke, mature cysts are unable to undergo any further development in the intestine in which they are produced, so that under normal circumstances, they do not hatch there. Sellards and Theiler have been able to produce acute infection of kittens by intrarectal injection of cysts.

Development of *E. histolytica* from the precystic form to the fully-mature quadrinucleate cyst proceeds in the lumen of the bowel. The whole process only occupies a few hours and the quadrinucleate cyst can survive in the bowel about two days, but, according to Yorke and Adams, there is some substance in the fæces which prevents further development. Fluid is necessary for excystation. From a fully-mature quadrinucleate cyst one quadrinucleate amœba emerges which subsequently divides after nuclear division into eight uninucleate individuals.

Culture.—After many unsuccessful attempts, the cultivation of *E. histolytica* on artificial media was effected by Boeck and Drbohlav in

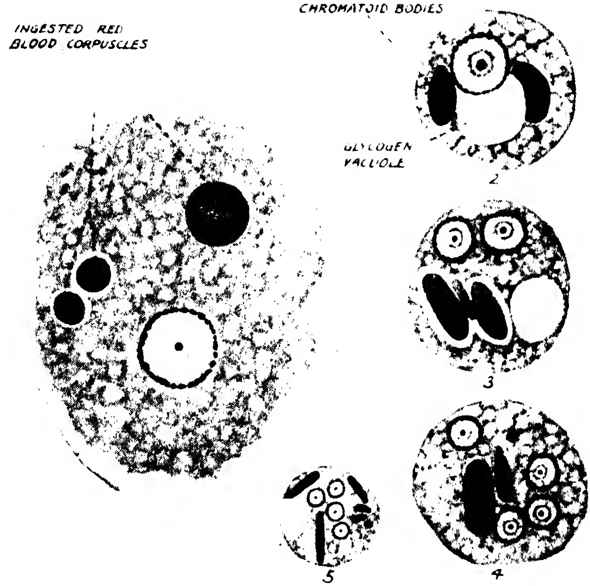


Fig. 189.—*Entamœba histolytica.* × 2,500. (*After Dobell.*)
1, Active amœboid form with ingested red blood-corpuscles. 2, Uninucleate cyst. 3, Binucleate cyst. 4, Quadrinucleate cyst. 5, Quadrinucleate cyst, small race, 6·6 μ in diameter. Note central distinct karyosome in the nucleus.

1925. They use solid blood-agar or solidified egg-slopes covered with Locke's solution (*see* p. 1040). The addition of a pinch of finely-powdered rice starch (collar starch) to each tube of the medium greatly aids the growth of the amœbæ, which ingest the granules with avidity. Recently these methods have been simplified by the introduction by Dobell and Laidlaw of a serum slope in place of the original egg-medium. The cultures are kept at 37° C. and must be reinoculated every two to four days. Subcultures which have been maintained for one hundred and fifty generations are still capable of producing amœbic dysentery when injected into kittens. In blood-agar cultures, and similarly in egg cultures, if the starch is withheld from a subsequent subculture and fresh blood is introduced, the entamœbæ will ingest red blood-corpuscles. Cultures may be obtained either from the active vegetative forms or from the cysts; in the latter case even after the

fæces have been passed for as long as nine days. Dobell has recently shown that in culture there is some manner of symbiosis between this amœba and a bacterium, and that the presence of the latter is necessary for the encystment of the amœba in culture (convivium). This amœba is extremely sensitive to emetine, which destroys it in culture in a strength of one in five million within four days. The disease—amœbiasis—can be reproduced in cats, dogs, and monkeys (*Macaca rhesus*) and even in the guinea-pig and rat by injection of cultures. The amœba of the monkey (*E. histolytica macacarum*) has been shown by Dobell to be identical with that of man. In the kitten (or cat) the infection is usually severe, so that the whole surface of the large intestine becomes infected with amœbæ, and, should the animal survive long enough, bacterial invasion of the blood-stream takes place. Metastatic

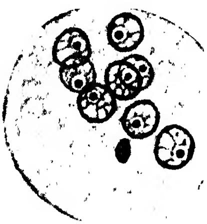


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Fig. 190. *Entamœba coli.* 2,500.
(*After Dobell.*)
1, Cyst with eight nuclei. Active amœboid stage with ingested food material. Note characteristic nucleus with eccentric karyosome.

abscesses in the liver are frequent and this has also occasionally been noted in the dog.

As *Entamœba dispar*, Brumpt recognizes a "physiological species" morphologically indistinguishable from *E. histolytica*, but not capable of engulfing red blood-corpuscles. It produces four nucleated cysts, is non-pathogenic to man and pathogenic only in a mild degree when injected into cats. It apparently lives in the fæces and does not invade the bowel-wall. It is not regarded as a distinct species by most observers.

Entamœba coli (*Grassi*, 1879) (Fig. 190).—*E. coli* is on an average larger than *E. histolytica*, but is subject to great variation in size. The size of the active stage of the organism may vary from 10 to 40 μ; as a rule it is 20–30 μ in diameter. Its movements are usually more sluggish than those of *E. histolytica;* the sudden extrusion of pseudopodia is never seen and the organism does not move across the slide, but remains in one locality. The cytoplasm is bulky and granular, and is usually charged with food vacuoles containing various objects such as bacteria, and even cysts of other protozoa

like *E. histolytica*, *Giardia*, *Isospora*, but never with red blood-corpuscles or tissue elements. There is not the differentiation of the cytoplasm into ectoplasm and endoplasm as occurs in *E. histolytica*. *E. coli*, in fact, leads a commensal existence in the fæces of the large intestine and does not live in the bowel-wall. It is of a greyish colour and this, with the large number of food vacuoles containing bacteria and other objects, serves to distinguish it from *E. histolytica*. Sometimes the vacuoles resemble fissures.

Compared with that of *E. histolytica* the nucleus is large, coarse, and easily visible in the unstained state. The chromatin granules on the nuclear membrane are relatively coarse, while other granules occur on the linin network. The karyosome which is larger than that of the nucleus of *E. histolytica* is eccentric in position and is surrounded by a clear area limited by granules.

Though these nuclear characters are seen in perfectly fresh specimens, as in the case of *E. histolytica*, they are frequently lost in individuals which are in the slightest degree degenerate.

Like other entamœbæ, *E. coli* reproduces by binary fission. Prior to encystation the amœbæ undergo a considerable reduction in size, with the result that the precystic forms can with difficulty be distinguished from those of *E. histolytica*.

Cysts.—The cysts (Fig. 190, *1*) exhibit a considerable variation in size, 10–30 μ ; and there is little doubt that, like *E. histolytica*, *E. coli* is a composite species, consisting of a number of races distinguishable by the dimensions of their cysts. The resting nucleus within the cyst bears the same characters as does that of the active form. The single nucleus, which is at first present in the cyst, divides by binary fission into two, four, and eight, the nuclei progressively diminishing in size. The mature cyst is octonucleate, though it must be remembered that immature binucleate and quadrinucleate cysts occur, and occasionally supernucleated cysts with sixteen nuclei. The cytoplasm of the cyst contains a variable amount of glycogen, which is most abundant in the binucleate form, and may be demonstrated with iodine solution. Chromatoid bodies are not always present, appearing more generally as small granular or rod-like bodies, especially in the binucleate stage. In mature octonucleate cysts they are, as a rule, absent, though when present they are usually in the form of pointed threads or splinters, thus differing from the stouter rod-shaped bodies with blunted ends found in *E. histolytica*.

The *life-history* of *E. coli* is similar to that of *E. histolytica*, save that the large vegetative forms inhabit the fæces, instead of the tissues of the host. *E. coli* may be cultivated upon the same media as used for *E. histolytica*, but with great difficulty.

E. coli infections are not affected by emetine.

Incidence of E. coli.—This organism is common in man, both in temperate zones and in the tropics ; it is probably more readily found in the fæces of dysenteric cases and is present in about 15 per cent. of normal individuals. Various animals, especially monkeys, harbour species of entamœbæ resembling *E. coli*. Those of the monkey are not improbably identical with the human form.

Councilmania lafleuri was the term proposed by Kofoid and Swezy for an amœba in human fæces which they thought differed from *E. coli* ; but this view has not gained general acceptance.

Entamœba gingivalis (Gros, 1849) (Fig. 191).—The amœba of the mouth was the first amœba discovered in man. Bass and Johns (1915) considered

it to be the cause of pyorrhœa alveolaris, but this has been disproved. It is a small amœba showing great variations in size—from 10 μ to 25 μ in diameter. Endoplasm and ectoplasm are rather sharply differentiated, and the cytoplasm is filled with food vacuoles and peculiar inclusions of a greenish, refractile appearance. The nucleus is spherical and vesicular, varies in diameter from 2·5 μ to 3 μ, and is slightly smaller in proportion to the rest of the organism than is the nucleus of *E. histolytica* or *E. coli*. The

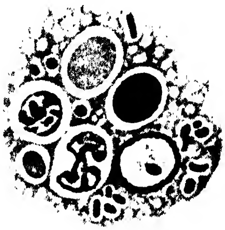


Fig. 191.—*Entamœba gingivalis*: active amœboid form with eccentric nucleus and ingested bodies. × 2,500. (*After Dobell.*)

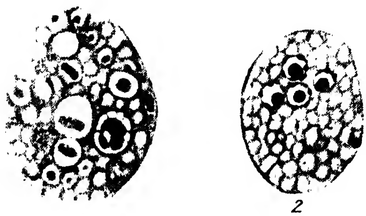


Fig. 192.—*Endolimax nana*. × 2,500. (*After Dobell.*)

1, Active amœboid form. 2, Quadrinucleate mature cyst.

Fig. 193.—*Iodamœba bütschlii*. × 2,500. (*After Dobell.*)

Active amœboid form with ingested micro-organisms. 2, Mature cyst, "iodine cyst," containing large iodine-staining glycogen mass.

nuclear membrane is very definite and is dotted over with granules of chromatin. Apart from the peculiar greenish refractile bodies, which may be the remains of salivary corpuscles or polymorphonuclear cells, *E. gingivalis* usually contains large numbers of bacteria. The amœba probably reproduces by binary fission, although all the stages have not been observed. It is also probable that this species does not form cysts, though bodies believed to represent this stage have been described.

Endolimax nana (Wenyon and O'Connor, 1917) (Fig. 192).—This species is of importance in so far that its quadrinucleate cysts, which are sometimes spherical, resemble the smaller cysts of *Entamœba histolytica*. It is commonly

present in normal fæces, and has been recorded in some 33 per cent. of dysenteric and diarrhœic stools. It is a small amœba, 6–12 μ in diameter, with characteristic vesicular nucleus and a large and irregularly-shaped karyosome. It probably inhabits the small intestine, living upon the intestinal contents. The *cysts* (Fig. 192, *2*) are characteristic structures of the same size as the active form, and contain, when mature, four nuclei, a few visible refractile granules, but no vacuoles or chromatoid bodies. Glycogen cannot always be demonstrated in the cysts, though it is most commonly found in the binucleate forms. They vary in shape from a typical oval to a sphere; very small individuals are 6 μ in diameter. Occasionally they contain peculiar inclusions resembling long and filamentous rods or granules, and are then liable to be mistaken for cysts of *Giardia intestinalis*.

Like *Entamœba coli*, *Endolimax nana* is non-pathogenic and infections with it are not amenable to emetine treatment.

E. nana may be cultured to a limited degree on Boeck's and Drbohlav's medium.

TABLE SHOWING DIFFERENTIAL CHARACTERS OF THE COMMONER INTESTINAL AMŒBÆ

Entamœba coli.	*Entamœba histolytica.*	*Endolimax nana.*
Size: 18–40 μ.	20–30 μ.	6–12 μ.
Morphology: No distinction between endo- and ecto-plasm.	Granular endoplasm; clear ectoplasm.	Granular and rather vacuolated cytoplasm.
Ingests bacteria, other protozoa, etc.	Ingests red cells, tissue cells, etc.	Ingests bacteria food granules.
Nucleus distinct in fresh specimens. Coarse chromatin granules on nuclear membrane. Eccentric karyosome surrounded by coarse ring.	Nucleus inconspicuous in fresh specimens. Fine chromatin granules on nuclear membrane. Central karyosome surrounded by delicate ring.	Clear nuclear membrane and massive, irregular karyosome.
Sluggish movement with granular pseudopodia.	Active movement with clear, blunt pseudopodia.	Sluggish movement with clear pseudopodia.
Multiplication: By binary fission in fæces. Encystment and formation of 1, 2, 4, and 8 nucleated spherical cysts, 10–30 μ in diameter.	By binary fission in *intestinal* wall. Encystment and formation of 1, 2, and 4 nucleated spherical cysts, 7–15 μ in diameter.	By binary fission in fæces. Encystment and formation of 1, 2, and 4 nucleated oval cysts 8–10 μ in length by 4–5 μ in breadth.
Chromatoid bodies typically not present in the mature cyst.	Chromatoid bodies especially present in the mature cyst.	Chromatoid bodies not present in the cyst.

Iodamœba bütschlii (Prowazek, 1912) (Fig. 193).—The cysts formerly described as "iodine cysts" or "I. cysts" in human fæces are now definitely known to belong to this amœba. A similar organism has been described from the dejecta of monkeys and pigs. *I. bütschlii* is a small amœba, intermediate in size between *E. coli* and *E. nana*. It measures from 9 to 20 μ in diameter, but very small individuals 5 μ in size have been recognized.

In form and habit it is very like a small specimen of *E. coli*. The cytoplasm is filled with food vacuoles containing bacteria and other food particles. The nucleus, which is often quite invisible in organisms containing much food, has a diameter of about one-fifth to one-fourth of that of the whole organism; it is vesicular, and has a moderate-sized central, intensely-staining karyosome, 2–3·5 μ in diameter. The nuclear membrane is well developed. Between it and the karyosome is a clear zone occupied by a layer of small granules. *I. bütschlii* feeds chiefly upon the micro-organisms of the large intestine, which it inhabits, but the active forms, or trophozoites, are much less commonly encountered than are the cysts. Multiplication of this amœba is by binary fission; but, according to Dobell, a reduction in size of the precystic stage does not take place.

The cysts are remarkable uninucleated structures, very frequently irregular in outline, but typically spherical or oval, and measuring 9–12 μ in diameter.

Fig. 194.—*Dientamœba fragilis*, uninucleate and binucleate forms. × 2,500. (*After Dobell.*)

Owing to the irregularities in their shape, they are often difficult to measure with certainty, but 6–16 μ may be taken as extremes of the largest diameter. They contain numerous refractile granules formed of a substance known as *volutin*, and, almost invariably, a comparatively large and dense glycogen mass, most readily seen when the cysts are suspended in iodine solution. Sometimes two or even three separate masses may be found in the same cyst. The cyst nucleus, eccentrically placed, is of a comparatively large size, 2–2·5 μ. The karyosome, which is centrally situated in the nuclei of active precystic amœbæ, gradually passes during encystment to the periphery and becomes a large compact mass in contact with the nuclear membrane.

The mature uninucleate cysts of this amœba, save for the disappearance of the contained glycogen, undergo no further changes outside the human body.

I. bütschlii occurs in about 5 per cent. of fæces, most commonly in those who have been in the tropics, and not infrequently in association with *E. histolytica*.

Infections showing both the active forms and the cysts of *I. butschlii* are extremely amenable to emetine and emetine-bismuthous iodide. How this drug acts it is difficult to say, for it is without effect upon *E. coli* and *E. nana* infections. This amœba has been cultivated on egg-medium by Thomson and Robertson.

Dientamœba fragilis (Jepps and Dobell), 1918 (Fig. 194) is a very small

amœba, 3·5–12 μ in diameter, its usual size being 8–9 μ. It lives in the large intestine. It is actively motile, with marked differentiation between ecto- and endo-plasm. The pseudopodia are lobed and indented. It is a rare amœba, and few cases of infection with it have so far been described. Each individual is typically binucleate. In size the nucleus ranges from 0·8 μ to 2·3 μ; it is spherical, the karyosome being large and composed of a number of granules embedded in a plastin matrix. After leaving the body the amœba quickly degenerates. It would appear to live exclusively upon bacteria and other small micro-organisms. It is doubtful if cysts have been seen.

Parasitism.—Most of the intestinal amœbæ of man are liable to be invaded by a fungus known as *Sphærita;* this consists of small spherical masses of a coccus-like body which is refractile in a living condition and occurs within vacuoles of the cytoplasm.

INTESTINAL FLAGELLATES

Tricercomonas intestinalis (Wenyon and O'Connor, 1917). Synonym, *Enteromonas hominis* (Fonseca, 1915).—*T. intestinalis* (Fig. 195, J-L) is a minute and very active flagellate, almost pyriform in shape, measuring 4–10 μ in length by 3–6 μ in breadth. The posterior end is drawn out to a fine point. The nucleus is single and vesicular, and three flagella of equal length arise from a blepharoplast on its membrane: a fourth also arises from it but runs to the posterior extremity of the body, ending as a terminal lash. The combined action of these flagella is to produce a "hovering effect." The cysts are of small size and closely resemble fungus spores; they are oval in outline with a distinct cyst-wall and contain iodophilic refractile bodies. Cultivation of the parasite can easily be effected on Boeck and Drbohlav's Locke egg-medium.

Embadomonas intestinalis (Wenyon and O'Connor, 1917) (Fig. 195, G-I), is a small, active flagellate of oval shape, 4–9 μ in length and 3–4 μ in breadth inhabiting the intestinal canal of man. There are two flagella, the anterior being the longer and thinner; the posterior projects from a mouth situated somewhat laterally at the anterior end. These flagella act independently of each other, thereby imparting a peculiar jerky movement to the organism. In shape it is ovoid, possessing a blunt anterior and a pointed posterior extremity. The cytoplasm is vacuolated and contains ingested bacilli. The round nucleus occupies the anterior end of the body. The cysts are pear-shaped, 4·5–6 μ in length, and when viewed in the fresh state appear to be structureless; when they are stained, certain nuclear structures can be made out.

This parasite has been cultured on egg-medium; it has apparently no pathological significance.

Chilomastix mesnili (Wenyon, 1910). Synonym, *Tetramitus mesnili* (Fig. 195, D-F)—The parasite also occurs in the large intestine and resembles *Trichomonas hominis* in general shape and size. It has three long anterior flagella, but is devoid of the undulating membrane and axostyle. It possesses a large mouth, occupying two-thirds of the body-length, with a contained flagellum which, in common with the three anterior organs, arises from a granule situated anteriorly to the spherical nucleus. The posterior extremity is drawn out to a fine point. The cytoplasm is vacuolated and may contain bacteria, which form the food supply. These organisms vary much in length, but average 14 μ in length by 5–6 μ in breadth. Division probably takes place by longitudinal fission. In formed stools the lemon-shaped cysts appear, and

PLATES XXIX AND XXX

INTESTINAL PROTOZOA

Row A. *Entamœba histolytica.* (Unstained.)

1. —Active vegetative form with ingested red blood-corpuscles: granular endoplasm and clear ectoplasm.
2. Precystic form: Note large nucleus with central karyosome.
3. Immature cyst with two nuclei and contained chromatoid rods.
4. Mature cyst with four nuclei, vacuole and chromatoid rods.
5. Uninucleated cyst of the minuta form.

Row A_1. *Entamœba histolytica.* (Stained Weigert's Iodine.)

1. Precystic form. Note diffuse iodine-staining substance.
2. —Immature cyst with two nuclei and chromidial rods.
3. Mature cyst with four nuclei, iodine vacuoles and chromidial rods.
4. Quadrinucleated cyst of the minuta form.

Row B. *Entamœba coli.* (Unstained.)

1. Active vegetative form with characteristic nucleus, blunt pseudopodia and protoplasmic vacuoles with food material.
2. Precystic form with characteristic nucleus.
3. —Immature stage with two nuclei and vacuole.
4. Mature cyst with eight nuclei.

Row B_1. *Entamœba coli.* (Stained Weigert's Iodine.)

1. —Active vegetative form with vacuoles and ingested food material.
2. —Precystic form.
3. —Immature cyst with two nuclei and vacuole.
4. —Mature cyst with eight nuclei.

Row C. *Endolimax nana.* (Unstained.)

1. Active vegetative form with one nucleus and many small vacuoles.
2. Mature cyst with four nuclei.

Iodamœba bütschlii. (Unstained.)

3. —Active vegetative form with one nucleus and large vacuole.
4. —Mature cyst with one nucleus and large vacuole.

(Continued overleaf.)

PLATES XXIX AND XXX

INTESTINAL PROTOZOA (*Continued*).

Row C_1. *Endolimax nana.* (Stained Weigert's Iodine.)

1.—Active vegetative form with one nucleus and protoplasmic granules.
2.—Mature cyst with four characteristic nuclei and iodine-staining substance.

Iodamœba bütschlii. (Stained Weigert's Iodine.)

3.—Active vegetative form with one nucleus and iodine-staining vacuole.
4.—Mature cyst with one nucleus and iodine-staining vacuole.

Row D. *Giardia intestinalis.* (Unstained.)

1.—Active form with sucking disc.
2.—Active form (side view).
3.—Cyst with two dividing nuclei.
4.—Four nucleated cyst (end-on view).

Row D_1. *Giardia intestinalis.* (Stained Weigert's Iodine.)

1.—Active form with sucking disc.
2.—Active form (side view).
3.—Cyst with two dividing nuclei.
4.—Four nucleated cyst (end-on view).

Row E. *Trichomonas hominis.* (Unstained.)

1.—Active form with undulating membrane and supporting rod.

Chilomastix mesnili. (Unstained.)

2.—Active form with peristome and contained flagellum.
3.—Pear-shaped cyst of above.
4, 5, 6.—Various forms of *Blastocystis hominis*.

Row E_1. *Trichomonas hominis.* (Stained Weigert's Iodine.)

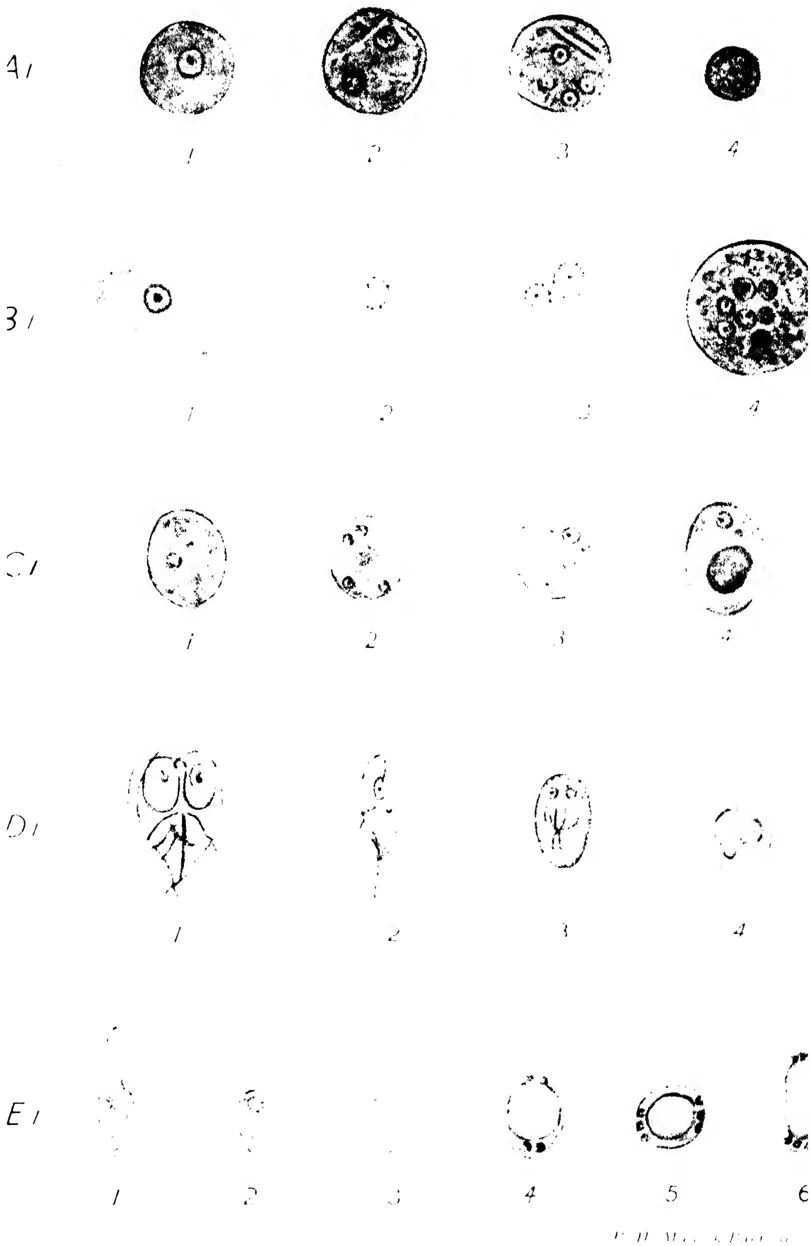
1.—Active form with undulating membrane and ingested red blood-corpuscles: the latter is an occasional occurrence.

Chilomastix mesnili. (Stained Weigert's Iodine.)

2.—Degenerated form as it commonly appears when acted upon by iodine.
3.—Pear-shaped cyst of above with nucleus and peristome.
4, 5, 6.—Various forms of *Blastocystis hominis*.

HUMAN INTESTINAL PROTOZOA (unstained).

PLATE XXIX



HUMAN INTESTINAL PROTOZOA (stained with Weigert's iodine).

vary in length from 7 to 10 μ; they contain a single nucleus, and show vestiges of a mouth structure as in the free form. In fresh preparations the cysts have to be differentiated from the yeasts of similar size and shape which are frequently present in fæces.

In freshly voided discharges *Chilomastix* has an active, jerky movement, which distinguishes it from the more deliberate rotatory action of *Tricho-*

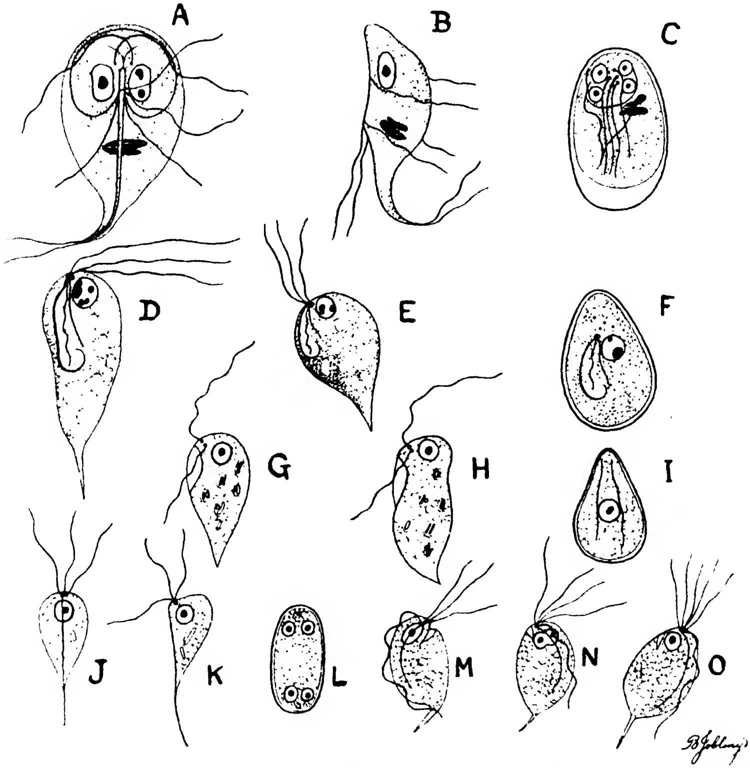


Fig. 195. The flagellates of the human intestine. ($\times$ 2,000). (*After Wenyon.*)

A-C, *Giardia intestinalis*, free and encysted forms; D-F, *Chilomastix mesnili*, free and encysted forms; G-I, *Embadomonas intestinalis*, free and encysted forms; J-L, *Tricercomonas intestinalis*, free and encysted forms; M-O, *Trichomonas hominis*, forms with three, four and five flagella.

monas. Infections with this parasite are very persistent, though there is no evidence that it is pathogenic. Recently it has been cultured on artificial media, as in the case of *Trichomonas hominis.*

Trichomonas hominis (Davaine, 1860) (Fig. 195, M-O).—This common intestinal flagellate of man inhabits, often in enormous numbers, the large intestine and cæcum. Its body is pear-shaped, 10–15 μ in length by 7-10 μ in breadth. A spherical nucleus is situated at the anterior end, and just anterior to this are placed the blepharoplasts from which arise the long free

flagella; these are directed forwards, while a thicker one passes backwards and forms the border of an undulating membrane, beyond which it is continued as a free flagellum. A small aperture near the anterior end represents the mouth or cytostome. A stiffening rod supports the undulating membrane and arises from the blepharoplast. Running down the middle of the body is a second skeletal rod, known as the axostyle. The cytoplasm is vacuolated and contains bacteria and food granules. According to the number of free flagella (3, 4 or 5), three varieties of *Trichomonas* are known. The one with four free flagella is most commonly encountered.

These flagellates progress rapidly by lashing movements proceeding from the three anterior flagella, while the undulating membrane causes the parasite to revolve on its longitudinal axis. The parasite is also capable of a certain amount of amœboid movement, especially evident in degenerating individuals.

Reproduction is effected by longitudinal fission. When the various organs are completely duplicated, the body of the flagellate splits and gives rise to two daughter individuals. No encysted forms are known, though it seems they must be present at some stage.

The abundance of *T. hominis* in diarrhœic conditions has led some observers to regard it as pathogenic to man. Wenyon, on examination of material from cases of intestinal infection with this organism, found definite evidence of invasion of the intestinal wall by the flagellates. He has pointed out that guinea-pigs infected with *T. caviæ* often show ulceration of the large intestine.

Another species, *Trichomonas buccalis*, occurs in the mouth-cavity and on the surface of the tonsil, and a third, which inhabits the vagina, is known as *Trichomonas vaginalis*, and is found in 10 per cent. of women. According to Wenyon and O'Connor, intestinal infections with *Trichomonas* are very persistent. The parasite may be present for weeks, disappear from the stools mysteriously, and return just as mysteriously at some later period. There is no evidence that it is pathogenic. Its presence in diarrhœic stools is probably merely a coincidence as it finds in the liquid fæces a congenial medium for multiplication. In dysenteric stools containing blood these flagellates not infrequently ingest red blood-corpuscles.

Varieties of *Trichomonas* occur; those with three, four or five anterior flagella have been termed *Tri- Tetra-* and *Penta-trichomonas*. *Trichomonas hominis* can be cultivated on blood-agar and Locke's fluid, similarly to *E. histolytica* (p. 1040), for many generations. Subinoculations must be made every few days.

Giardia intestinalis (Lambl, 1859). Synonyms, *Lamblia intestinalis*, *Giardia lamblia* (Stiles, 1915) (Fig. 195, A-C).—This parasite lives in the upper part of the small intestine, particularly the duodenum. In shape it resembles the half of a pear split longitudinally, and it measures 12–18 μ in length by 6 μ in breadth. The ventral surface has a concave sucking disc, with a raised edge, at the anterior end. The posterior extremity tapers into a tail and terminates in two flagella. There are four pairs of flagella, arising from a series of blepharoplasts. Two axostyles pass down the centre of the body. Two oval nuclei are situated at the anterior end. The flagellate swims rapidly, swaying from side to side. *Giardia* reproduces itself by a very complicated process of binary fission. The cysts may occur in enormous numbers in the fæces. At first binucleate, certain complicated changes proceed inside the cyst-wall, which result in the formation of four nuclei, duplication of all

the structures, and finally two completely new individuals. They are then very characteristic structures, 14 μ in length. The cytoplasm is quite transparent, and the structures contained therein can be defined with precision. The presence of the axostyles, which form a sort of dividing line within the cyst-wall, gives it a distinctive appearance and serves to distinguish it from cysts of amœbæ (Fig. 195, C). When examined in iodine solution, these cysts stain a faint yellowish-brown colour and the cytoplasmic contents tend to shrink back from the cyst-wall.

Infections are very persistent, so that cysts may be found in the stools for many years. Under certain conditions, it is thought by some observers, this parasite may assume a pathogenic rôle. It is said to have been seen in bile removed from the gall-bladder at operation and is commonly found in the duodenal juice obtained by tubage. It has not been artificially cultured.

Species of *Giardia* occur in rats, mice, cats, dogs and other animals.

INTESTINAL COCCIDIA

The Coccidia are intracellular protozoa, in whose life-cycle there is an alternation of generations, in which an asexual cycle—schizogony—alternates with a sexual cycle—sporogony. In the latter a single zygote which becomes encysted as an *oocyst* eventually produces a number of sporozoites which are included in masses within smaller cysts, or *sporocysts*.

The life-history of a typical member of the genus *Eimeria*, such as that found in the liver of the rabbit, is actually very similar to that of a malarial parasite. It was from the study of this parasite that Pfeiffer in 1892 predicted in such a remarkably accurate manner the life-cycle of the malaria parasite within the mosquito. The life-history of *Eimeria schubergi* of the centipede, *Lithobius forficatus*, is very similar to that of the rabbit, and may be taken as an example. The young parasites, or sporozoites, are liberated from a sporocyst in the intestinal tract and penetrate epithelial cells, where they grow into large schizonts, characterized by a large vesicular nucleus and a karyosome. When full-grown the nucleus divides by repeated fission till a variable number of daughter-nuclei are produced. The schizont now divides into as many merozoites as there are nuclei. The cells burst, the merozoites are set free, and entering other cells develop in one of two ways, either into schizonts again or into gametocytes. There is sexual differentiation of the latter ; in the male the protoplasm is clear, but in the female it is crowded with reserve food material.

The male gametocyte develops further ; the nucleus divides repeatedly, forming many secondary nuclei, which develop into microgametes—small, slender bodies provided with two flagella. The host cell then bursts, liberating the microgametes, which endeavour to enter the female cell or macrogamete. When one such has effected its entrance, the fertilized macrogamete, which is now known as a zygote, secretes a tough membrane and becomes an oöcyst, thus preventing entrance of any other microgametes. The nucleus of the penetrating microgamete fuses with the female nucleus, forming a synkaryon. The zygote then breaks up into four sporoblasts, each then becomes surrounded by a tough envelope, the sporocyst, within which the protoplasm divides to form two sporozoites. Consequently, when sporogony is complete, the original oöcyst contains four sporocysts, each containing two sporozoites. In order to develop further the oöcyst must pass out with the fæces and be swallowed by a new host, whereupon the tough membranes dissolve, liberating the sporozoites.

Coccidia are common parasites of vertebrates. Several instances are on record of the finding of oöcysts of coccidia, resembling those of *Eimeria stiedæ* of the rabbit, in human livers post-mortem. The parasite in human liver has been named *E. gubleri* (Guiart, 1922). Since Woodcock and Wenyon's discovery of the oöcysts of *Isospora* in human fæces in 1915, and Dobell's work on the same subject (1919), it is known that the oöcysts of at least three different coccidia—one belonging to the genus *Isospora* and two to the genus *Eimeria*—are occasionally found in the fæces of man.

Human Coccidiosis

Isospora hominis (Railliet and Lucet, 1901). Synonym. *Isospora belli* (Wenyon, 1923). (Fig. 196, *1, 2.*)—More than 150 cases of infection

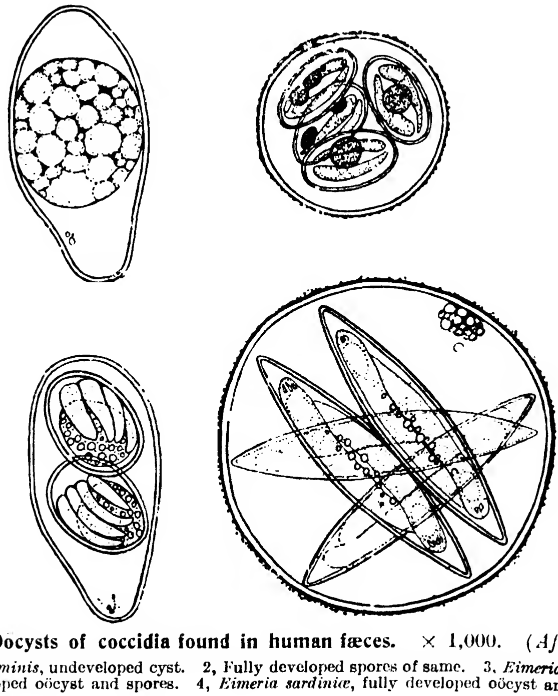


Fig. 196.—Oöcysts of coccidia found in human fæces. × 1,000. (*After Dobell.*)

1, *Isospora hominis*, undeveloped cyst. 2, Fully developed spores of same. 3, *Eimeria clupearum*, fully developed oöcyst and spores. 4, *Eimeria sardiniæ*, fully developed oöcyst and spores.

have been recorded with this organism in man. Though undoubtedly parasitic in man, it is not seriously pathogenic, though in the case described by Connal and also the one treated by the Editor (*see* p. 568) there was continuous and debilitating diarrhœa of six weeks' duration, associated with numerous Charcot-Leyden crystals and pus cells in the fæces and a high eosinophilia in the blood. Most of the cases come from the Eastern Mediterranean, but the Editor's was infected in the West Indies. The schizogonic cycle of development in the intestine is unknown. The oöcysts are an elongated oval in shape, with a tapering extremity, and vary in length

from 18–33 μ, while their length is 12·5–16 μ; the oöcyst-wall is perfectly clear and colourless. These oöcysts are usually discharged with the zygote in an unsegmented condition, but occasionally after its segmentation into sporoblasts. In the fæces outside the body the zygote segments to form

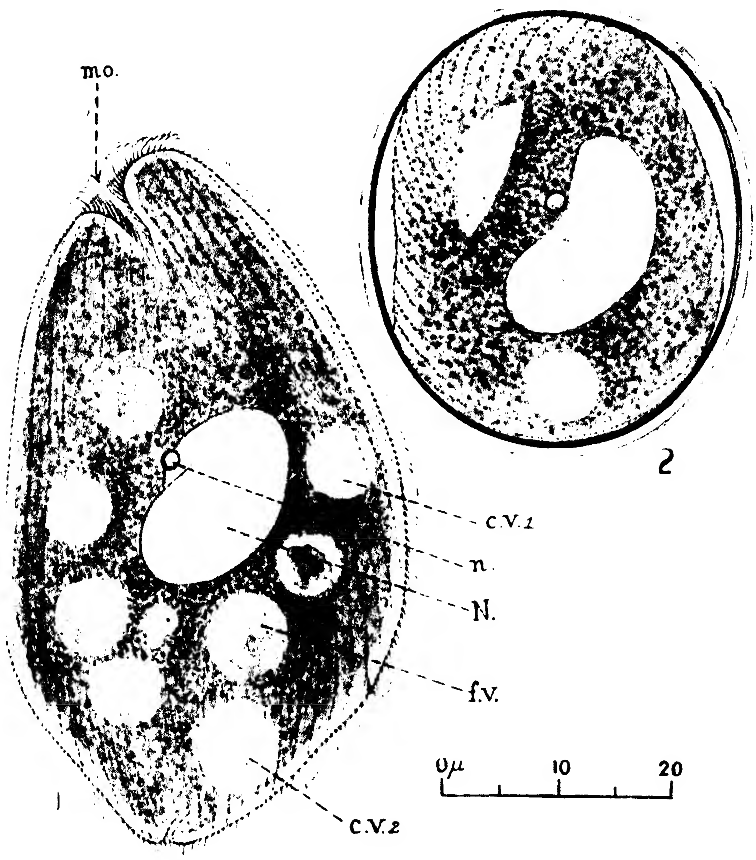


Fig. 197.—*Balantidium coli.* × 1,200.
(*After Dobell; by permission of Medical Research Council, Report No.* 51.)

1, Living animal; N., meganucleus; n, micronucleus; c.v.1, anterior contractile vacuole; c.v.2, posterior contractile vacuole; f.v., food vacuole; mo., mouth.
2, Encysted form, showing nuclei, posterior contractile vacuole, and remains of cilia.

two ovoid sporoblasts which quickly become enclosed in sporocysts, each measuring about 14 μ in length by 7–9 μ in breadth, and each eventually containing four sporozoites.

With regard to the coccidia of the genus *Eimeria* in human fæces, Thomson and Robertson pointed out that these are actually parasites of fish and that the oöcysts are passed unchanged through the human intestine after ingestion.

Attention is given to these organisms because they were formerly thought to be parasitic in the human intestine.

Eimeria clupearum (Thélohan, 1892) (*E. wenyoni* (Dobell, 1918)) (Fig. 196, *3*).—The oocysts are passed in the fæces with spores and sporozoites fully developed. The oöcysts are approximately spherical in shape, with a diameter of 22 μ; the outer surface is rugose, the inner smooth and lined with a delicate membrane. The four oval sporocysts within the oöcyst-walls measure 10 μ by 7 μ, and each contains two typical sporozoites. The oöcysts of this coccidium are found in the intestine in 100 per cent. of herrings, mackerels and sprats.

Eimeria sardinæ (Thélohan, 1890) (*E. oxyspora* (Dobell, 1918)) (Fig. 196, *4*). This coccidium has been found in human fæces on several occasions. The spherical oöcysts measure 36 μ in diameter, and have their contents completely differentiated into four sporocysts, 30 μ in length by 7·5 μ in breadth. Each in turn contains two long slender sporozoites.

As in the foregoing species this coccidium occurs in the testes of sprats and to a lesser extent in the soft roes of adult herrings.

BALANTIDIUM

One important Infusorian occurs in man—the ciliated protozoon, *Balantidium coli* (Malmsten, 1857). This parasite is oval in shape, and is of variable size. It may measure 30–200 μ in length by 40–60 μ in breadth, though the average length is 50–70 μ. There are probably various races, distinguished by their size.

The body is clothed with a thick covering of cilia. There is a large kidney-shaped macronucleus with a small micronucleus approximated to it. The protoplasm contains two contractile and a number of food vacuoles, and there is at the anterior end an opening—the *peristome*—leading into the mouth or cytostome, and a posterior *cytopyge* or anus. Nutrition is effected by ingestion of solid particles. The cuticle is longitudinally striated. (Fig. 197, *1*.) The parasite reproduces itself asexually by transverse fission. Conjugation takes place by approximation of two individuals and by the exchange of certain nuclear elements; after this has been effected the conjugants separate. Encystment occurs (Fig. 197, *2*); the cysts, which are slightly ovoid, measuring 50–60 μ in diameter, are passed in the fæces, the infection being transmitted by their ingestion.

The parasite has been cultured artificially on human serum diluted with saline and kept at 30–37° C. Frequent subinoculations are necessary.

B. coli sometimes burrows into the submucosa causing a dysenteric condition known as balantidial dysentery or balantidiasis (*see* p. 564). The ciliate is a normal inhabitant of the large intestine of pigs, and those who are in attendance upon them are liable to infection. It has been found in the mesenteric glands, as well as in the ulcers. It is a very active and obvious parasite, and may occasionally be found in diarrhœic, as well as in blood and mucous stools.

Infection with this organism has been recorded from France, Germany, the Philippines, and elsewhere. The parasite also occurs in monkeys and allied species, in ruminants, and other animals in captivity. It may be the cause of death in monkeys in zoological gardens. Infection is conveyed from one host to another by means of the cysts.

PROTOZOA OF THE BLOOD

1. *Trypanosomes*

The structure of the trypanosome body is of a uniform type, though subject to variation in minor details. The body is slender; the anterior[1] end tapers gradually to a fine point, while the posterior generally terminates

[1] The terms "flagellar" and "aflagellar" may be used to designate the extremities of the body, instead of the terms "anterior" and "posterior" respectively, which are here employed strictly with reference to the mode of progression.

more bluntly (Fig. 198). The general shape of the body is that of a curved, flattened blade.

The nucleus (trophonucleus) is situated centrally; the kinetoplast is usually placed posteriorly to the nucleus, but is sometimes closely approximated to it. Certain exceptions to this rule are known, namely, *T. rhodesiense* (p. 163), *T. brucei* and some multiplicative forms of *T. lewisi.* The axoneme, the axial filament of the flagellum, arises from a blepharoplast, and passes forwards along the margin of the undulating membrane; in some cases it may end with the undulating membrane at the anterior extremity of the body; but more usually it is continued forwards into the flagellum. Trypanosomes in which the axoneme extends beyond the anterior end of the body into it are said to have a free flagellum.

Trypanosomes multiply by binary fission. The kinetoplast (blepharoplast and parabasal) first divide. This is followed by division of the nucleus and formation of a new flagellum and membrane. The body then divides longitudinally from before backwards.

Trypanosomes occur as blood parasites in all classes of vertebrates. Many

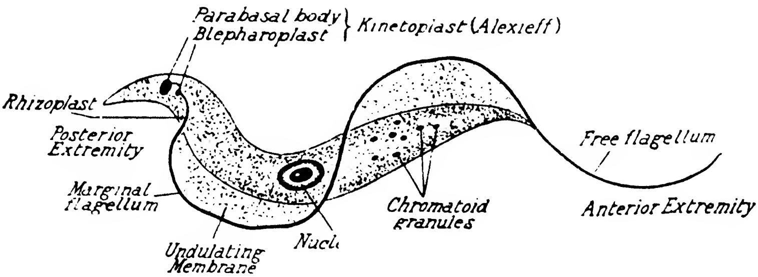


Fig. 198.—Sehema of *Trypanosoma* (*After Dobell.*)

wild animals harbour them. They are very specific to a particular host and are in most cases harmless parasites.

Transmission.—Except in the case of *Trypanosoma equiperdum* which passes from horse to horse during coitus, trypanosomes are transmitted from one vertebrate host to another by blood-sucking invertebrates, usually insects, and in the cases of fish, leeches. In some cases, as for instance *Trypanosoma evansi*, the transmission is purely mechanical, a fly after feeding on an infected animal within a few minutes bites an uninfected one, thus inoculating trypanosomes which have remained alive in or on its proboscis. In most cases, however, transmission is associated with a definite developmental cycle in the fly, so that, after an infective feed, there is an incubation period before the fly again becomes infective. Infectivity is always dependent on the final production in the fly of a special type, known as the metacyclic trypanosome.

There are two main types of development. In one development commences in the stomach, the developing forms spreading forwards to the proboscis and salivary glands, or development is confined entirely to the proboscis, while in the other development commences in the stomach, the developing forms passing backwards to the hindgut. The first type of development is referred to as taking place in the *anterior station*, and the

second type as in the *posterior station.* In the case of anterior development, the metacyclic infective trypanosomes are inoculated during the biting act, while in the case of the posterior development, the metacyclic infective trypanosomes escape in the fæces of the insect and gain entrance to the mouth of the vertebrate and bring about infection in that way.

The pathogenic trypanosomes of Africa are transmitted by species of *Glossina* in which three types of development in the anterior station occur. In the case of *T. gambiense, T. rhodesiense* and *T. brucei*, the ingested trypanosomes commence to develop and multiply in the stomach, where finally a long slender type of trypanosome is produced. This form migrates forwards to the proventriculus and thence to the proboscis and salivary glands. In the salivary glands it becomes transformed into crithidial forms which attach themselves to the glandular cells. They are converted into metacyclic trypanosomes which resemble those originally present in the blood. These trypanosomes are inoculated with the saliva when the fly bites. In the case of *T. congolense* there is at first a stomach phase of development, but the long slender trypanosomes pass forwards to the proboscis only, and not to the salivary glands. It is in the proboscis that crithidial forms and finally the metacyclic trypanosomes are produced. Finally, in *T. vivax* there is no stomach phase of development, the trypanosomes developing only in the proboscis, where the crithidial and metacyclic forms are evolved.

In all other instances of known transmission of trypanosomes associated with development in intermediate hosts evolution is in the posterior station. Thus in *T. cruzi*, transmitted by reduviid bugs, such as *Panstrongylus* (*Triatoma megistus*), development commences in the stomach and proceeds in the hindgut, where numerous crithidial forms are produced. Finally metacyclic trypanosomes are evolved which escape from the intestine of the bug in its fæces. From what is known of the transmission of the rat-trypanosome, *T. lewisi*, by the flea, and the sheep-trypanosome, *T. melophagium*, by the ked (*Melophagus ovinus*), it seems probable that infection of the vertebrate with *T. cruzi* is brought about by the ingestion of the fæces of the bug.

Cultivation.—Trypanosomes can be cultivated in certain blood-media. Those of cold-blooded vertebrates and birds and the non-pathogenic species of mammals such as *T. lewisi, T. theileri, T. melophagium*, etc., are easily cultivated in N.N.N. medium or some of its modifications. The pathogenic forms like *T. gambiense, T. rhodesiense, T. brucei, T. congolense, T. vivax* and *T. evansi*, are very difficult to cultivate in this medium, though in a primary culture they will change in form and survive for many days. Subculture is difficult to obtain. In more complicated media it is sometimes possible to carry on cultures for many generations. On the other hand, *T. cruzi* resembles the non-pathogenic trypanosomes in being more readily cultivated.

Generally speaking trypanosomes in cultures tend to develop along the lines of the cycle in the invertebrate. Crithidial forms are produced, and after these have multiplied for some time there again appear trypanosome forms which probably correspond with the metacyclic trypanosomes developed in the invertebrate host.

Trypanosoma gambiense (Dutton, 1902).—This trypanosome never occurs in the blood of man in great numbers. Sometimes it can be more readily found in the fluid obtained by puncture of an enlarged lymphatic gland, or in the cerebro-spinal fluid. It varies much in length and breadth during different stages of its existence ; as a general rule, it measures 13–39 μ

in length, by 1–3 μ in breadth. (Fig. 199, *1*.) The polymorphism in the blood of mammals is one of the most characteristic features of this trypanosome. Three types are normally recognized—short stumpy forms without free flagellum, long slender forms with free flagellum, and intermediate forms.

The parasite is found, not only in the blood, but in the lymphatic glands, the cerebro-spinal fluid, and the substance of solid organs, especially the brain. Most laboratory and domestic animals can be infected with this trypanosome, but baboons (*Cynocephalus*) and the sooty mangabey monkey (*Cercocebus fuliginosus*) are refractory. *Trypanosoma nigeriense* is considered to be merely a local variety of *T. gambiense*.

Development of T. gambiense in Glossina palpalis.—Trypanosomes are ingested by the glossina and during the first few days of their residence in

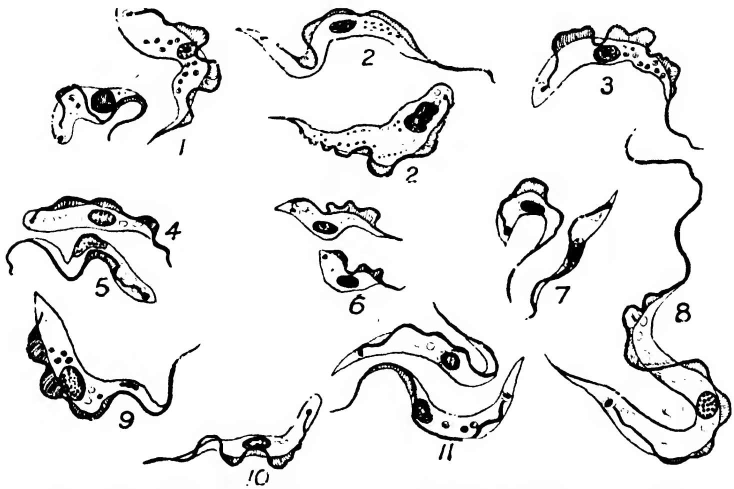


Fig. 199.—Various trypanosomes of man and animals. × 1,300.
(*After Wenyon.*)

1, *T. gambiense*; 2, *T. rhodiense (brucei)*; 3, *T. evansi*; 4 and 5, *T. uniforme*, *T. vivax*; 6, *T. congolense*; 7, *T. cruzi*; 8, *T. theileri*; 9, *T. equinum*; 10, *T. equiperdum*; 11, *T. lewisi*.

the stomach of the fly, multiplication proceeds, trypanosomes of various shapes and sizes being produced, until by the seventh to the tenth day they exhibit a very wide range of form. From the tenth to the twelfth day onwards, long slender forms appear in great number, and gradually migrate towards the proventriculus of the fly, in which organ they become the predominant type. The proventricular forms migrate to the salivary glands, where they assume a crithidial shape and attach themselves to the wall of the ducts. Development in the salivary gland proceeds for a period of from two to five days, when there are produced metacyclic trypanosomes, which are the forms infective for man.

Under optimum conditions the complete cycle of development in the tsetse fly takes at least eighteen days. Moreover, of the total number of flies fed on blood containing trypanosomes, multiplication of the organism takes place in only 8 per cent., and in a still smaller proportion only are metacyclic infective forms produced.

Reservoir-hosts.—In the laboratory most forms of the South African antelope have been experimentally infected from the bites of infective glossinæ, but under natural conditions it is improbable that all forms of antelope act as reservoir-hosts of this trypanosome. The swamp-dwelling forms, particularly "the situtunga," *Limnotragus spekei*, have fallen under suspicion. In addition to these, all domestic animals, even sheep and dogs, may be naturally infected, but they succumb as a rule so rapidly that they cannot be considered so much a source of danger as are the wild game.

Trypanosoma rhodesiense (Stephens and Fantham, 1910).—In the blood of man *T. rhodesiense* is indistinguishable from *T. gambiense*, the same three types being recognizable. In order to differentiate it, it is necessary to subinoculate the strains into laboratory animals, preferably the rat. In this host a change takes place in the position of the nucleus; whereas in *T. gambiense* it is always anterior to the kinetoplast, in *T. rhodesiense*, in a varying proportion of the trypanosomes, it assumes a position close to the kinetoplast or, in a very few cases, actually posterior to this structure. The proportion of posterior nuclear forms, which are notably shorter than the normal, rarely constitutes more than 5–6 per cent. of the total number of trypanosomes. (Fig. 199, *2*.)

Thomson and Robertson (1927) demonstrated that certain arsenical preparations administered to animals infected with trypanosomes which had lost their posterior-nucleated forms, instantly caused their reappearance. Yorke (1911) found that goats and horses infected with this trypanosome developed an interstitial keratitis of the eyes, in which trypanosomes could be demonstrated in the interstitial tissues outside the blood-vessels.

Some authorities regard *T. rhodesiense* as representing the human strain of *T. brucei*, as it is morphologically identical with it while in Uganda the International Commission claimed that posterior nuclear forms may occur rarely in *T. gambiense* infections, and that probably *T. rhodesiense* is merely the former trypanosome transmitted through a different species of glossina, or a more virulent race of it; but this view has not gained general acceptance.

Geographical distribution.—This trypanosome has a limited geographical distribution, being confined to Northern Nyasaland, North-Eastern Rhodesia, Portuguese East Africa, and the Southern Sudan, but is thought to be extending its range. Its pathogenicity is greater than that of *T. gambiense*; it is more resistant to treatment, and more virulent to laboratory animals.

Development in G. morsitans.—As far as is known, the development of *T. rhodesiense* in *G. morsitans* and other tsetse flies is identical with that of *T. gambiense* in *G. palpalis*. Probably it is this species which is transmitted by *G. swynnertoni* in Mwanza (Tanganyika Territory).

Trypanosoma (Schizotrypanum) cruzi (Chagas, 1909). Synonym, *T. escomeli.*—Occurs in the blood of man in Brazil, Venezuela, and Argentina, causing a disease known as Chagas' disease. The development of this trypanosome (Fig. 200) differs materially from that of any of the preceding, by the method of multiplication in the body. When present in the blood-stream it is dimorphic, some forms being broad and others narrow. The posterior end is sharp and wedge-shaped, while the parabasal body is large; individuals measure about 20 μ in length. (Fig. 199, *7*.) As Robertson has pointed out, they invariably assume a C-shaped attitude in the peripheral blood. This trypanosome was first discovered in the bug (*Panstrongylus*) by Chagas, and subsequently the infection was found in man.

Certain individual trypanosomes leave the blood-stream and enter the

muscles, especially those of the heart, or it may be the cells of the brain or other organs, and there undergo a series of rapid binary fissions during which they assume a leishmania form. Multiplication of these leishmania forms is so rapid that soon a quarter of the tissue is invaded. Four or five days later the leishmania forms become elongated and assume a crithidial form,

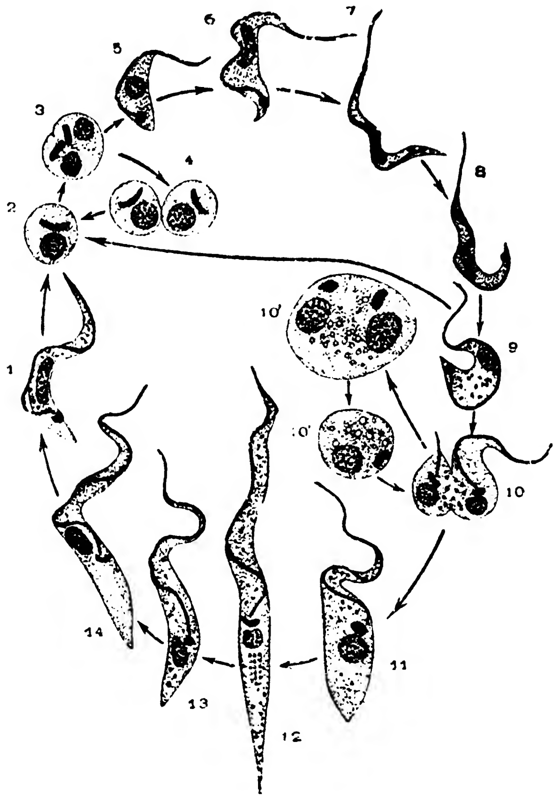


Fig. 200.—Evolutionary cycle of *Trypanosoma cruzi* **: 2–9 in man or other vertebrate ; 9–14 in** *Panstrongylus*, *Triatoma* **or** *Cimex*. × 1,500. (*After Brumpt.*)

1, Metacyclic trypanosome infecting vertebrate; 2, 3, 4, schizogony in organs; 5–9, transformation of adult trypanosome (9); 10, crithidial form about to divide in small intestine; 10[1], leishmania forms frequent in the proventriculus; 11–14, progressive transformation of crithidia forms into metacyclic trypanosomes (1) in hindgut.

and are transformed once more into trypanosomes, which make their way through the tissues and regain the blood-stream.

Trypanosomes are taken up from the blood of man by a reduviid bug, *Panstrongylus* (*Triatoma megistus*), and undergo an elaborate development; this can occur either in the larval, nymphal, or adult stage of the insect. They pass from the stomach into the small gut and become transformed into crithidial forms and in this state continue to multiply rapidly. Eight

to ten days later the metacyclic or infective trypanosomes make their appearance, and pass out in the fæces of the insect. Inoculation of the parasite into man would seem to take place through the ingestion of fæces or the rubbing of fæcal matter into the wound made by the bug, though some investigators claim to have transmitted the disease through the bites of *Panstrongylus* and *Triatoma*. (Fig. 200.)

Under experimental conditions the parasite can be inoculated into rats, mice, rabbits, guinea-pigs, and monkeys, and can pass through the mucous membrane of the mouth or conjunctiva, which must have undergone some slight injury or abrasion.

Reservoir-hosts.—Armadillos—*Dasypus novemcinctus, Euphractus sexcinctus*, and *Cabassous unicinctus*—appear to be natural carriers of infection. The cat has been found naturally infected, and Robertson has discovered this trypanosome in the blood of the opossum (*Didelphis paraguayensis*) in Honduras, 2,000 miles distant from the hitherto-recognized endemic zone of this disease in man. Numerous bugs can act as definite hosts. *Triatoma infestans T. sordida, T. vitticeps, T. dimidiata* var. *maculipennis* are found naturally infected in Brazil; *Rhodnius prolixus* and *Eratyrus cuspidatus* in Venezuela. The bug, *Triatoma protracta*, a species common in California, and extending as far north as latitude 41° (Salt Lake City), harbours a flagellate like *T. cruzi*, but the human disease is unknown in this area. Under experimental conditions other species of *Triatoma* of the United States can be easily infected, as well as the cosmopolitan *T. rubrofasciata* ; in fact, it is probable that all species of *Panstrongylus* and *Triatoma* and allied genera are susceptible. Under laboratory conditions, Brumpt has obtained development of, and persistence of the parasite in, *Cimex hemiptera* (*rotundatus*), *C. lectularius*, *C. boueti*, and *C. hirudinis*, also the African ticks, *Ornithodorus moubata* and *O. savignyi*.

The multiplicity of the vicarious hosts of *T. cruzi* would certainly indicate that the disease it gives rise to could spread in many countries if all conditions were favourable ; the reduviids are so easily infected that it is possible to infect 100 per cent. of them at all stages of their existence ; moreover, once infected they remain so for life, they themselves not suffering from the effects of thus being parasitized. Probably the trypanosome is naturally a parasite of armadillos, etc., and only occasionally becomes inoculated to man.

Trypanosoma lewisi (Kent, 1879), is a parasite of the rat all over the world, and is very numerous, as a rule, in the blood-stream (Fig. 199, *11*) at the height of an infection. That it may occasionally infect man was demonstrated by Johnson (P. D.) 1933, in a Sikh child of five months old, in Malaya. The trypanosomes were visible in large numbers in the blood for five days, after which they disappeared. The infection was associated with pyrexia and a large increase of the small lymphocyte cells. It is, however, generally considered to be non-pathogenic. Individual trypanosomes vary very considerably in size and appearance during the multiplicative phase, which passes on in about a week to a chronic phase, in which the trypanosomes measure, on an average, 24 μ. The nucleus is situated slightly anterior to the middle point of the body. The parasite undergoes development in *Ceratophyllus fasciatus*, *Xenopsylla cheopis*, and other fleas, as well as in the rat-louse, *Polyplax spinulosa*. The rat-flea is the chief carrier. The trypanosomes make their way into the epithelial cells of the stomach, in which they become spherical and grow in size. The nucleus divides repeatedly, and with portions of adherent protoplasm forms young trypanosomes. These

escape from the cell and pass into the hindgut after two days, where they become crithidial forms. Eventually they escape as small metacyclic trypanosomes in the excreta. These are ingested by the rat, which licks up the flea fæces or devours the entire flea. Trypanosomes appear in the blood after an incubation period of six days.

2. *Leishman-Donovan Bodies*

The parasites belonging to this genus occur in man in kala-azar, oriental sore, and the muco-cutaneous disease of South America. The parasite of kala-azar is known as *Leishmania donovani;* that of the similar disease in Brazil has been tentatively named *L. chagasi*, and that of oriental sore *L. tropica*. It is supposed by some that the parasite of Mediterranean kala-azar which is associated with the disease in dogs is a distinct species—*L. infantum*. The canine form is known as *L. caninum*, while that of the South American disease has been named *L. braziliensis, or L. americana*. There are no morphological differences between the parasites from all these diseases, and they cannot be differentiated from one another except by some serological reactions. Cutaneous leishmanial injections have been found also in the dog, brown bear and horse. Probably tissue changes produced after inoculation into hamsters may indicate specific differences. Hindle has shown that in these animals *L. infantum* produces periarthritic swellings of the extremities and tail, thus differing from *L. donovani*. The Leishman body is a small, round, oval, or, sometimes, cigar-shaped body varying in diameter from 1 to 3 or 4 μ. It consists of a minute mass of cytoplasm enclosed by a delicate membrane. Within the cytoplasm is a nucleus and a kinetoplast consisting of parabasal body and blepharoplast; further there arises a rhizoplast, a rod-shaped body, which represents the axoneme of the flagellum of the flagellate and which develops in cultures and also in the body of certain sandflies.

The parasites in the body occur, sometimes in large numbers, in the large endothelial cells, macrophages or clasmatocytes. These cells in kala-azar are found with the contained parasites in all parts of the body, particularly the spleen, bone-marrow and liver and, in oriental sore and the South American disease, in the skin and mucosæ. The parasite, the Leishman-Donovan body, is actually the rounded stage of a flagellate having the structure of a leptomonas, a fact which is shown by its development into flagellates of this type in artificial culture media.

Life-history.—The life-history of members of the genus *Leishmania* is essentially that of insect flagellates of the genus *Leptomonas*. A typical form, *Leptomonas ctenocephali* of the dog-flea, multiplies in the hindgut as an elongated flagellate and finally produces in the rectum small, round leishmania bodies which, escaping in the fæces, are eaten by the flea larvæ. In members of the genus *Leishmania* the same leishmania forms occur, but in the tissues of man they multiply by binary fission. It was shown first by Rogers that these forms developed in culture media into leptomonad flagellates like the corresponding stages of the flagellate of the dog-flea. Since the successful reproduction of oriental sore in man by the inoculation of crushed-up sandfles (*Phlebotomus*) by Sergent and his co-workers, attention has been directed towards these insects. It has been found that in the stomach of insects of this genus, both *Leishmania tropica* and *L. donovani*, taken up from man, develop rapidly into the typical elongate leptomonad forms, and that these tend to spread forwards to the biting parts of the fly (buccal cavity,

proboscis). It has been shown by Adler and Theodor that when such infected flies feed into a sterile fluid through a rabbit-skin membrane, flagellates are infected into the fluid. Both in the sandfly and in N.N.N. culture medium (p. 1039), the rounded leishmania form first increases in size and then develops a flagellum. By further growth and active multiplication there is produced the elongate leptomonas form with its long flagellum. In the fly many of the flagellates become attached to the wall of the anterior part of the stomach. On account of the resemblance of the various forms to those of the flagellate of the dog-flea or other insects, authorities consider that the parasite of kala-azar and oriental sore should be included in the same genus (*Leptomonas* or *Herpetomonas*.)

The fully-developed elongate flagellates are 14–20 μ in length by 2 μ in breadth. The flagellum is 16 to 24 μ in length. The flagellates move actively with the flagellum in front, and in cultures tend to agglomerate in clusters

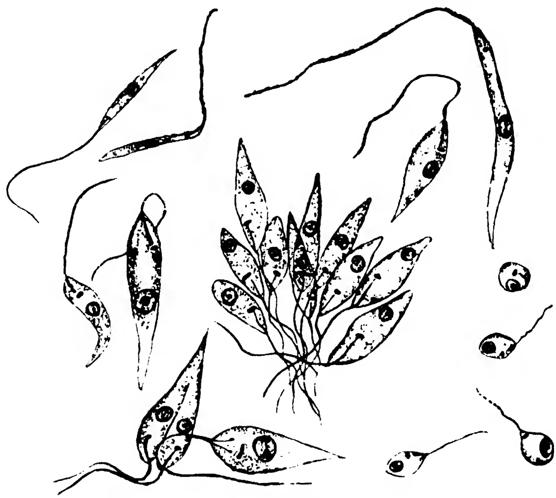


Fig. 201.—Developmental forms of *Leishmania donovani* from the leishman body to the crithidial stage, and clumping of the flagellated organisms. $\times$ 2,000. (*After Wenyon.*)

(rosettes), the flagella being directed centrally. The culture medium originally used by Rogers was made by adding material from spleen-puncture to slightly acidified citrate-of-soda solution. It is now known that the parasites will grow better in the liquid of condensation of blood-agar medium (N.N.N. medium). A small quantity of infected material from a human case of kala-azar or oriental sore is added to the water of condensation. The tubes are incubated at 22–25° C. In two or three days flagellates of various shapes appear in the liquid. These multiply for two to three weeks, after which it is necessary to subculture into fresh tubes, if the culture is to be maintained. Cultures may be obtained from any tissues containing parasites, even the peripheral blood, but it is essential that bacterial contamination should be excluded. (Fig. 201.)

Nomenclature of hæmoflagellates.—There are four types of flagellate—

leishmania, leptomonas, crithidia and trypanosome—names derived from generic titles. Certain flagellates have only leishmania and leptomonas stages. If confined to insects alone, they belong to the genus *Leptomonas*; if occurring in both insects and vertebrates to the genus *Leishmania*. Other flagellates have leishmania and crithidia stages. All these are confined to insects and are included in the genus *Crithidia*. Others again have leishmania, crithidia and trypanosome stages. If in insects alone, they are termed *Herpetomonas*, but if in both insects and vertebrates they belong to the genus *Trypanosoma*.

3. *Malaria Parasites* (*Plasmodiidæ*)

There are four species of *Plasmodium* which are found in man, viz. *P. vivax*, *P. ovale* (p. 63), *P. malariæ* (p. 62), and *P. falciparum* (p. 63).

Closely allied species have been found in the higher apes and in certain monkeys, e.g. *Plasmodium pitheci* in the orang-outang (*Simia satyrus*), *P. kochi* in *Cercopithecus*, *P. knowlesi*, and *P. inui* in *Macaca*, *P. cynomolgi* in *Inuus cynomolgus*, and *P. brazilianum* in *Brachyurus calvus* in Brazil. A form, *P. reichenowi*, which produces crescents has been found in the chimpanzee and the gorilla. The relationship of these parasites to certain aberrant forms described in man is a debatable point. Monkey malarial parasites have been shown to develop in anopheles mosquitoes by Clark in Panama, Green in Malaya, and Sinton and Mulligan in India.

Plasmodium knowlesi from *Macaca irus* from Malaya rather resembles *P. vivax* in man, and produces Schuffner's dots. It can be inoculated into man, in whom, after an incubation period of nine to nineteen days, it produces a mild type of fever with a tendency to spontaneous cure.

Similar parasites are found in birds, bats, and squirrels and cold-blooded animals such as lizards. In small birds, sparrows and finches, an analogous and pathogenic parasite is known as *Plasmodium* (*Proteosoma*) *præcox*, and in owls and crows as *P. danilewskyi*. Other species have been described from birds. In contradistinction to the human and monkey parasites, transmitted by anopheline mosquitoes, the bird parasites are transmitted by culicine mosquitoes, such as *Culex fatigans* and *Aëdes ægypti*. In the red blood-cell of the bird, certain species displace the cell nucleus, in this manner differing from *Halteridium*. Brumpt has shed a new light upon the development of the plasmodidæ by the discovery of *Plasmodium gallinaceum*, a malaria parasite of fowls which develops in *Aëdes ægypti*. In this bird, as shown by Kikuth and James, pigmentless schizonts form in the endothelium of the brain, kidney, lung, liver, heart, and bone-marrow. Kikuth has also described pigmentless endothelial schizonts of *P. cathemerium* in experimentally-infected canaries.

A form of pigment-producing parasite is found in the blood of certain reptiles and is known as *Hæmocystidium*. The parasites, which are related to *Halteridium* of birds, are of a large size.

The following is a detailed description of the human malaria parasites:—

The benign tertian parasite, *Plasmodium vivax* (Plate III, facing p. 64). —In its early stages this parasite assumes a distinct ring-form with large and conspicuous vacuole, and large nucleus, which is situated usually at the thinnest part of the ring; sometimes, though rarely, the nucleus is duplicated so as to form two dots in a signet ring. (These do not represent two distinct nuclei, but merely the original one broken into two fragments.) The diameter of the average ring is about 3 μ, though larger forms may reach to half the size of the containing corpuscle. As it grows, the trophozoite shows great

activity, changing its form and location in the corpuscle, insistently pushing out and retracting pseudopodia (Plate III). This amœboid movement persists during the growth and while the hæmozoin is being deposited, though in progressively diminishing degree; and explains the great irregularities seen in the contour of the parasite in stained specimens (Fig. 4, p. 60). The movement is entirely suspended by the time the parasite has reached its full development. The vacuole in which the nucleus is situated, and which is crowded with nutritive chromatin, becomes much smaller as the parasite develops. The parasite grows vigorously for about 40 hours, when it attains its full size; as it grows it obtains its nutriment at the expense of the red cell, and therefore marked changes take place in the protoplasm of the latter. When tertian-infected corpuscles are stained with Romanowsky's stain, the protoplasm is speckled with chromophilic particles—*Schüffner's dots*—which are at first very fine, but soon become coarser and more prominent. They are characteristic of *P. vivax* and also *P. ovale*. This is a feature of some diagnostic value, but in the very young phase of the parasite it is not always present. The dots are usually pinkish in colour and are much more prominent and consistent in artificially inoculated malaria (*see* p. 63). Another highly characteristic accompaniment of tertian infection is the considerable enlargement of the infected corpuscles. Sometimes they seem to be nearly twice the diameter of healthy ones; and usually the rim of corpuscular protoplasm surrounding the parasite has a "washed-out" appearance.

Schizogony.—The fully-formed schizont is more or less round in shape, being larger than a normal corpuscle and about 9–10 μ in diameter. The nucleus is fairly large, often lying near the periphery of the parasite, with the chromatin somewhat diffusely arranged. One or two small vacuoles may still be present. The first stage of schizogony consists of nuclear multiplication, the result of binary fission. The number of merozoites thus formed varies from 14 to 24. This process of multiplication takes 6–8 hours, when the merozoites are liberated from the corpuscle; the cycle therefore lasts for about 48 hours. Complete schizogony coincides with the occurrence of a rigor in the patient (Fig. 3, p. 59).

Gametogony.—After schizogony has continued for a certain period, some young trophozoites become sexual forms or gametocytes. It is stated that the latter can be recognized in the earlier stages as small solid forms. Growth is much slower, a gametocyte taking nearly twice as long as a schizont to become adult, and, moreover, no vacuole is developed in the cytoplasm. The growing parasite is less active, and hence it does not exhibit the manifold changes of form seen in the growing schizont. The quantity of pigment produced is also much greater, the granules of the macrogametocyte being more numerous and larger than in the adult schizont. The macrogametocyte (or female form) is much larger than the mature schizont, being 12–14 μ in diameter, while the microgametocytes (or male forms) are much smaller (Fig. 4, p. 60). There are other distinguishing features in the microgametocyte: the nucleus is large and diffuse, spreading across the body in the shape of a spindle; the cytoplasm is hyaline, and stains a lighter colour; while the nucleus of the macrogametocyte is small, compact, and stains more deeply, and the cytoplasm is granular, non-vacuolated, and stains an intense blue. As a rule, macrogametocytes are more numerous in the blood than microgametocytes.

Plasmodium vivax is capable of maintaining itself (after a single infection) in the human body for a period of about three years, after which it dies out.

Ovale tertian parasite, *Plasmodium ovale* (Plate III, facing p. 64) Stephens, 1922.—In 1922 Stephens described a new malaria parasite from East Africa, and named it *Plasmodium ovale.* It appears that it had previously been noted and described in 1914 by Ahmed Emin at Camaran in the Red Sea. In 1927 Stephens confirmed and extended his observations on a further case from Nigeria. In 1930 Yorke and Owen showed that the morphological features were preserved when the parasite was passed by direct blood inoculation from one person to another. James and Shute further succeeded in transmitting the infection through *Anopheles maculipennis,* so little doubt remains that this is a distinct and constant species. They have shown that its morphological features remain distinctive after repeated passages through insect and human hosts.

In 1933 further cases were reported from West Africa and by the Editor from Uganda. Recently it has been recognized that it has a wide distribution throughout Central Africa.

Plasmodium ovale has several features in common with the *P. vivax* and *P. malariæ.* It produces a tertian periodicity and it does not produce a marked enlargement of the host-cell. On the other hand, it has morphological features which closely resemble those of *P. malariæ,* but the red cells in which the parasite lies resemble those of benign tertian in producing Schüffner's dots. The small rings have no special features, but they lie in red blood-corpuscles which are usually oval (hence the specific name of the parasite) with irregular fimbriated margins. The half-grown forms are non-amœboid ; the pigment is brownish-black and granular, but the amount of chromatin and the distribution of the pigment in a lateral band are appearances which recall the quartan parasite. The infected corpuscle is so often oval in shape that this has special significance. The maximum number of merozoites is twelve, usually eight, lying in a decolorized, degenerated corpuscle with many Schüffner's dots. Occasionally a double infection of the cell is noted. The clinical course in man is usually mild, and the parasite tends to die out of its own accord after several paroxysms.

It has been pointed out by Mühlens and others that the fever produced by the parasite differs from benign tertian in producing paroxysms of fever which come on in the evening or at night. The character and arrangement of the pigment in the oöcyst in the stomach-wall of the mosquito seventy-two hours after feeding is distinctive, and the sporozoites in the salivary glands of infected anopheles are smaller than those of other malaria parasites.

Quartan parasite, *Plasmodium malariæ* (Plate III).—This parasite has a cycle in the peripheral blood of 72 hours. The young trophozoites usually have the signet-ring appearance, and are indistinguishable from the same stage of the tertian. At this stage it is capable of feeble amœboid movement ; hence the irregular forms so frequently met with in the tertian are not found in the quartan. Later, as soon as it becomes pigmented, all the amœboid movement ceases (Fig. 202), and it grows across the corpuscle, producing a characteristic ribbon or band-shaped appearance. Even the nucleus itself becomes elongated at this stage.

The changes produced in the corpuscle differ from those seen in benign tertian. The red cell does not enlarge, but tends to contract and becomes slightly smaller than the average. Schüffner's dots are not seen, but the quartan stippling consists of dots and points smaller and less distinct than the former, which stain by Romanowsky stains within five minutes, while the stippling is not demonstrable till after twenty minutes. According to James,

"*Ziemann's stippling*" should be the correct description. The hæmozoin is darker brown and coarser in appearance, and the oscillation of the pigment granules is less marked than in benign tertian.

Schizogony.—The adult schizont is distinctly smaller than the corresponding phase of the benign tertian, rarely exceeding 6·5 μ in diameter. The parasite does not occupy the whole of the red cell. Nuclear division *begins after the schizont has been growing for 48 hours, and takes place* comparatively slowly. The number of merozoites is small, varying from 6 to 12; their arrangement is symmetrical, giving rise to a daisy-head appearance. The individual merozoites are larger than in the benign tertian and average 1·75 μ in diameter. The segmenting schizont of the quartan parasite is more frequently seen in the peripheral blood than is the corresponding phase of the other forms. For this reason, and because of the easy visibility of the parasite in all its stages owing to the large amount of hæmozoin it carries, the quartan is the best form of malaria for the beginner to study.

Gametogony.—The growing gametocytes do not assume the band form of the growing schizont. The young macrogametocyte is heavily pigmented, and contains a smaller amount of chromatin than a schizont of the same

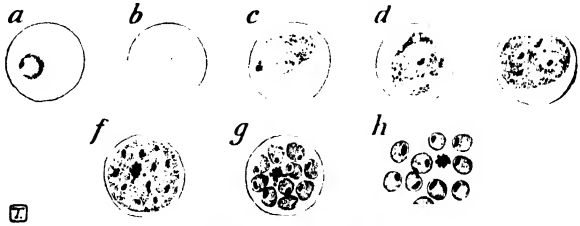


Fig. 202.—Quartan parasite, asexual cycle: stained.

size, but the microgametocyte has more chromatin and a lighter-staining cytoplasm. Adult quartan gametocytes usually occur but scantily in the protoplasm, the microgametocytes being particularly rare. The mature macrogametocyte completely fills the red blood-corpuscle, scarcely a rim of cell-protoplasm being visible, so that it looks at this stage as if it were a free and independent body floating about in the liquor sanguinis. The microgametocyte contains a very large amount of chromatin, and is slightly smaller than the female form. The quartan parasite is capable of maintaining itself in the human body for a longer period than the benign tertian and may persist for six or seven years or even (Mühlens) nineteen years (*see* p. 62).

The subtertian or malignant parasite, *Plasmodium falciparum* Blanchard (Plate III, A, facing p. 64). *Synonym : Laverania malariæ.*—A notable feature in the differentiation of this parasite is its much smaller size, the rings averaging 1·25 to 1·5 μ in diameter. The earlier phases, owing to their minuteness, and partly owing to the thinness of the cytoplasm, are difficult to see. (Fig. 203, *a*.) The rings are usually sharp and regular in outline, the chromatic nucleus being often divided into two—a very characteristic feature in stained preparations, which may distinguish it from the younger forms of the benign tertian parasite. Multiple invasion of individual corpuscles is often encountered much more frequently than in the benign infections, doubtless due to the prodigious number of parasites which may be present. Another characteristic of the young subtertian parasite is the

position in which many of them attack the host-cell, applying themselves to the margin or edge of the corpuscle. These are known as "accolé" or "appliqué" forms. Frequently they appear as short streaks of cytoplasm with red nuclear dots, giving them a bacilliform appearance, the vacuole not being visible (Plate III). Schüffner and Esseveld describe clumping of the red blood-corpuscles in blood-films reminiscent of the flocculation observed in blood-grouping. The parasitized cells are surrounded by non-parasitized erythrocytes.

At this stage, unless the observer has had a great deal of experience, the parasite is apt to be missed, for it may be the only form appearing in the peripheral circulation. As the development advances, the invaded corpuscles are filtered out by the capillaries and small arteries of the deeper viscera and of the bone-marrow; they are especially numerous in such organs as the spleen and the liver. In heavy infections a few more mature forms than the ring can be found, and very occasionally a fully-segmenting schizont. Rarely

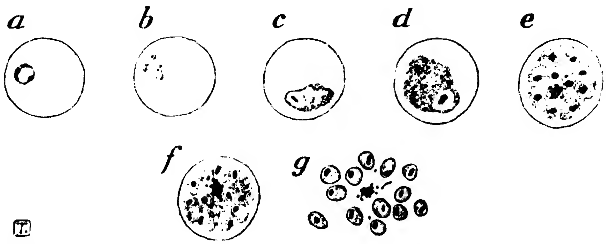


Fig. 203.—Evolution of the subtertian parasite: asexual cycle.

cases are met with in which all stages of schizogony may be observed in the peripheral circulation. As a rule, it is necessary to aspirate splenic blood, or to search the bone-marrow or viscera—liver, spleen, or kidney—immediately after death, in order to find examples of the more advanced stages of the parasite (Fig. 203, *c, d, e, f*). It is difficult to fix the duration of the life-span of these parasites, but it is probably one of 36 to 48 hours.

In the case of *P. falciparum* the size of the host-cell remains practically unaltered. Schüffner's dots do not occur, but occasionally other brick-red or pink dots, which are larger and more irregular in shape than Schüffner's, become apparent; they are usually known as Maurer's clefts. When seen in the fresh state the infected corpuscles have a slightly darker look, which is said to resemble old brass, and hence they have been referred to as "brassy bodies." The hæmozoin in the growing schizonts occurs in well-developed blocks, and usually appears as one dark and conspicuous mass.

Schizogony generally occurs in the capillaries of the internal organs. The adult schizont commonly measures 4·5–5 μ in diameter, and a large part of the host-cell is unoccupied. Nuclear division takes place rapidly, and the number of merozoites produced, even in the same infection, varies very greatly. They usually number from 8 to 24 (Fig. 203, *g*). The merozoites themselves are smaller than those of the benign tertian parasite, and average from 0·7 to 1 μ in size. Schizogony does not proceed at the same uniform rate as in the case of the other types. Apparently it may take anything from 36 to 48 hours to accomplish.

Gametogony.—The gametocytes of this parasite assume the well-known

crescent shape which has already been referred to (Fig. 5, p. 61), but it should be said that the term crescent is not absolutely correct, for the ends are not, as a rule, pointed; their shape, in fact, is much more like that of a sausage, with rounded ends. They are fairly large bodies, ranging from 9 to 14 μ in length by 2–3 μ in breadth. It is believed by some that a definite capsule is secreted around the crescent bodies (J. D. Thomson), and that they are produced mostly in the capillaries of the spleen and bone-marrow. The crescents are not seen at the onset of the infection, but once they begin to appear in the peripheral blood they generally tend to increase in numbers during the next few days. Being much less amenable to the action of quinine than are other stages or types of the malaria parasite, they may persist in the blood for as long as six weeks after the subsidence of the fever. According to Sinton, the life-span of the crescent is 30–60 days. However, it has been noted that quinine, if given sufficiently early in the course of a subtertian attack, may prevent the crescents from appearing in the peripheral blood. Crescents are readily killed off by plasmoquine and its compound with quinine (*see* p. 116), but are not affected by atebrin.

The two sexes can be distinguished. The *male* (microgametocyte) is broader than the female, while its nucleus is diffuse and may occupy the greater part of the body, but the contained hæmozoin is scattered throughout the cytoplasm. The *female* (macrogametocyte), the more slender of the two, has a small centrally-placed nucleus, while the hæmozoin tends to be concentrated round about it. When the crescent is mature the substance of the contained red blood-corpuscle is entirely used up, so that only the corpuscular envelope persists, and in this the parasite lies. Sometimes the outline of the cell may be observed staining faintly on the margins of the crescent; very rarely, twin or double crescents are seen in one corpuscle.

It is a singular fact that in many of the worst types of subtertian malaria—as that of tropical Africa—crescents are few in number, and in some instances cannot be found by ordinary examination. Plehn states that during a period of two years in Africa he only once saw the flagellated body produced from the crescents. On the other hand, when we meet with these African infections in England crescents are often seen, and in great abundance; at all events, this is a general experience. In primary infections under suitable conditions, crescents appear in the peripheral blood about the third week.

The young gametocytes can be distinguished from schizonts of the same age by their elongated shape, and by the fact that the pigment is scattered, and not aggregated into one mass. The nucleus is small and situated towards one end of the parasite, and usually extends as a cross line along one edge of the body in very much the same way as in the quartan. Subsequently the nucleus passes towards the centre of the body.

The subtertian parasite has a much shorter life in the human body than the two species previously considered; at the most a single infection survives from one month to one year.

According to James, strains of *P. falciparum* exist differing from each other greatly in virulence.

Abnormal appearances of the malaria parasites.—Quite frequently, mixed infections of two, and very rarely three, forms of parasite can be found in the same individual; the usual combination, however, is the benign tertian with the subtertian infection. The immature forms of both parasites may be found in the same microscopic field, but most usually one sees the various developmental stages of benign tertian parasite combined with the crescents of

the subtertian ; very rarely the two different species of parasites have been observed in the same cell. Combined infections of benign and quartan may also be encountered. Certain puzzling appearances have been noted by observers since the time of Schaudinn, which were thought by him to represent a further stage than those already described as denoting a process of parthenogenesis, but these were shown by J. D. Thomson to represent two schizonts (both possibly segmenting) infecting the same red blood-corpuscle. Combined infection of schizont plus male or female gametocyte, or even two gametocytes, within the same red cell, has also been observed. Double, triple, and even quadruple infections of the same red blood-corpuscles by subtertian rings are quite commonly observed in heavy infections.

Cultivation of the malaria parasites.—The cultivation *in vitro* of the malaria parasites was first effected by Bass, in 1911, and subsequently confirmed by the brothers Thomson.

Asexual multiplication of the parasites has been observed in three types of malaria, and in the case of the subtertian parasite as many as four successive generations have been cultivated in this manner. Sinton, too, has grown crescents of the subtertian parasite in artificial culture of blood after 10 days' incubation. Several interesting points have been observed in the morphology of the cultivated parasites. The number of merozoites formed during schizogony is considerably greater than in the parasite under natural conditions, while the growing parasites of the subtertian form show a remarkable tendency to clump together, a phenomenon not observed in the benign tertian type.

When malaria blood is cooled outside the body, the *flagellated body*, which is derived from sexual cells or gametocytes, is observed to develop, a process never occurring in flowing blood. This body is composed of colourless protoplasm with contained granules of hæmozoin pigment, and is carried around suspended in the plasma. The flagella (zoologically known as *microgametes*) usually number six or more. Their filaments are very delicate, moving rapidly, so that every now and again they break away and swim with rapid vibratile movements (Fig. 5, p. 61).

The gametocytes of the four species of human malaria parasites differ in shape, being oval or round in benign tertian, quartan and ovale, but crescentic in subtertian ; in the last-mentioned, also, the outline of the host blood-cell can often be distinguished. The " crescent " shows no amœboid movement, and contains needle-shaped hæmozoin particles in the centre ; in the *male* type the protoplasm is hyaline and the hæmozoin loosely arranged ; in the *female* it is faintly granular with the hæmozoin arranged in a well-defined ring. In benign tertian, quartan, and ovale the corresponding sexual cells, or gametocytes, develop from young ring forms circulating in the peripheral blood, while in the subtertian they are derived from the corresponding stages of the parasites contained in the red blood-corpuscles agglommerated in the capillary vessels of the internal organs.

It has been shown that injection of gametocytes into a non-immune individual does not produce malaria infection.

The microgametes are formed of two elements—a chromatic filament and a covering of protoplasm, and after they have broken away, the remains of the flagellated body consists mainly of hæmozoin granules and some residual protoplasm which is usually ingested by some wandering phagocytes.

Conditions favouring and retarding eruption of microgametes.—By exposing the freshly-drawn malaria blood droplet to the air with a slight aqueous

admixture, as by breathing on it before applying the cover-glass, it is generally easy to procure specimens of the flagellated body. In certain bloods exflagellation rapidly takes place ; in others, the opposite is the case.

The granular spheres, or female gametocytes, do not emit flagella but, becoming spherical, remain quiescent. The object of the microgametes is

Fig. 204.—Evolution of the malaria parasite in anopheles maculipennis. (*Adapted from Wenyon.*)

1. (*a*) Exflagellation of the male gametocyte ; (*b*) free flagellum (male gamete) ; (*c*) fertilization of the female gamete in *P. vivax*. (*Original preparation*). 2. Oökinete in *P. falciparum*. (The remainder of the cycle refers to this parasite.) 3. Zygote in stomach wall of *A. maculipennis* showing contained pigment. 4, 5, 6, Oöcysts in stomach wall, showing reticulated cytoplasm with rapidly dividing nuclei. 7. Mature oöcyst with mature sporozoites still attached to masses of cytoplasm into which the reticulum is breaking up. 8. Sporozoites from salivary gland.

when they have broken away, to approach and to endeavour to enter the granular spheres (female gametes). At one point on the surface of each of the granular spheres a minute papilla projects, and at this point one of the microgametes enters and, after momentarily causing perturbation in the contents of the sphere, comes to rest and vanishes from view (Fig. 204, 1, *c*). Although the sphere may again be energetically attacked, no second micro-

gamete can effect an entrance. This process, first observed in 1897 by MacCallum, constitutes the act of impregnation. Subsequently for a short time the granular sphere undergoes no apparent change. The impregnated female parasite is now known as the *zygote*. It soon becomes oval and elongated, then finally assumes a vermicular form, with the hæmozoin accumulating at the broad or posterior end, while the anterior end becomes pointed and hyaline. Then capable of independent movement, it is known as the *travelling vermicule*, or, technically, the *oökinete*.

Summary of the life-cycle of the Plasmodiidæ.—It is now convenient to summarize the life-cycle of the malaria parasites (*Plasmodidæ*) within the body of man, as well as their exogenous cycle outside the body within the mosquito. This description applies equally to all the four human species, as well as to the analogous species of *Plasmodidæ* found in birds. The life-cycle is commenced by inoculation of the sporozoites with the saliva of the mosquito in the act of biting. Thus introduced, the sporozoite pierces and

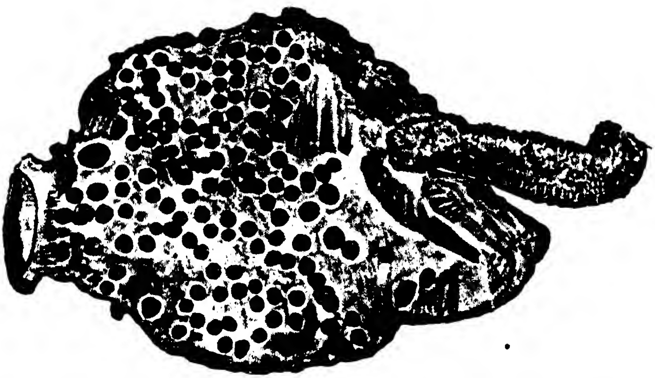


Fig. 205.—Stomach of *Anopheles maculipennis* infected with the oöcysts of *Plasmodium vivax*. (*Orig.*)

enters a red blood-corpuscle and soon becomes converted into a young parasite. Growth takes place at the expense of the cell. After a period of two or three days, the single nucleus, by repeated division, has multiplied to form a variable number of daughter-nuclei. The parasite then produces a corresponding number of merozoites and a mass of residual protoplasm which contains the characteristic pigment. By rupture of the cell, the merozoites escape into the plasma where, by attaching themselves to other red blood-corpuscles, they repeat the cycle. After several generations of merozoites have been produced, certain of them develop into *gametocytes*, or sexual cells, which, when mature, are of the same size as fully-grown *schizonts*, but contain more pigment granules and possess only a single nucleus. They are of two types, male and female, of which the latter has a dense and deeply-staining cytoplasm. They are capable of further development only if taken up by the specific kind of mosquito. In the male the nucleus divides, and the daughter-nuclei proceed to the periphery of the cell and become nuclei of a number of fine filaments endowed with motile powers, which break free from the cell as microgametes. In the meantime the female gametocyte becomes a macrogamete, and ready for fertilization by the microgamete. The

impregnated female gamete or zygote, is capable of independent movement, and (now termed an oökinete) bores its way through the lining epithelium of the mosquito's stomach, there encysts between the epithelium and the limiting membrane, and becomes an oöcyst (Fig. 205). The original nucleus now divides, and the protoplasm segments round the daughter-nuclei, forming a spongioplasm. Eventually the nuclei arrange themselves on the surface of

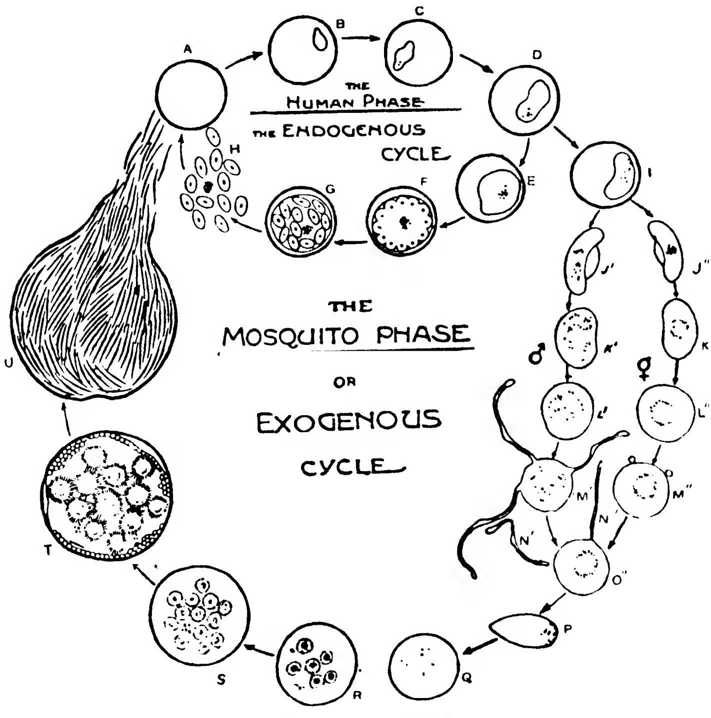


Fig. 206.—Schema showing the human and mosquito cycles of the malaria parasite.

A, Normal red cell; B, C, D, E, red cells containing young parasites; F, G, H, schizogony; I, young gametocyte; J', K', L', M', microgametocytes or male gametes; J", K", L", M", O", macrogametocytes or female gametes; N', N", microgametes; P, travelling vermicule (oökinete); Q, young zygote; R, S, oöcysts; T, oöcyst with plasmodial masses; U, mature oöcyst.

the cytoplasm; from this mass sporozoites are formed, each nucleus acquiring an appropriate quantity of cytoplasm. The oöcyst then bursts, setting free the sporozoites, some of which contrive to pass into the salivary glands of this insect, whence, with the salivary secretion, they once more enter the blood on which the infected mosquito is feeding. The whole body-cavity is filled with sporozoites, as was first demonstrated by Mühlens in 1921. He showed that after rupture of the cysts, sporozoites occurred in all parts of the body-cavity of anopheles, even legs and antennæ, and that only some of the sporozoites reached the salivary glands (Fig. 206).

Dissection of anopheles.—The investigator, on dissecting anopheles, should have no difficulty in recognizing malarial oöcysts, even under a low power of the microscope. They are spherical and very refractile, appearing to jut out beyond the stomach-cells. With a higher power ($\frac{1}{6}$ in. lens) the characteristic pigment can be seen in their interior; in *P. vivax* it is light-yellow, and in *P. falciparum* dark-brown in colour. There are various misleading appearances which one must learn to recognize, such as certain large body-cells—known as pancreatic cells—gregarine cysts, and even encysted larval trematodes, which occur in the stomach of these insects. The sporozoites

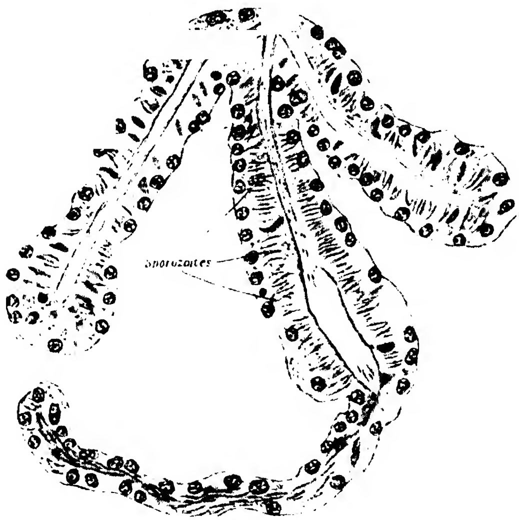


Fig. 207.—Salivary gland of *Anopheles maculipennis* **containing sporozoites of** *Plasmodium falciparum* **compiled from serial sections.** (*After Wenyon.*)

can be recognized as refractile bodies in the cells of the salivary glands (Figs. 207, 208).

Ross's black spores.—In some infected mosquitoes oöcysts may be encountered which differ in their appearance from normal ones at a similar stage of development. The cyst-wall in their case is filled with dark-brown or black masses, representing undoubtedly the degenerated cell-content, which has become chitinized. Some observers consider that these spores represent an invasion by a fungus which preys on the oöcysts.

Infectivity of anopheles.—Exact observations by Christophers have shown that, in the most favourable circumstances, at the maximum only about 4 per cent. of a suitable anopheline host (*Anopheles culicifacies*) are found infected under natural conditions. Roubaud indicates that *A. maculipennis* is a most propitious host for both *P. vivax* and *P. falciparum*; he found that

39·37 per cent. of the insects became infective with the former, and 50 per cent. with the latter parasite, when fed in captivity upon a suitable case. As regards natural infection of malaria in anophelines, many factors must necessarily be called into play. Amongst these the foremost are the season of the year at which the researches are carried out, whether malaria is rife at the time, and whether the insects have been captured in human habitations or in cattle sheds. Bentley in Bombay showed that 18 per cent. of *A. stephensi* were infected in August, but none in the dry season. Similar variations in

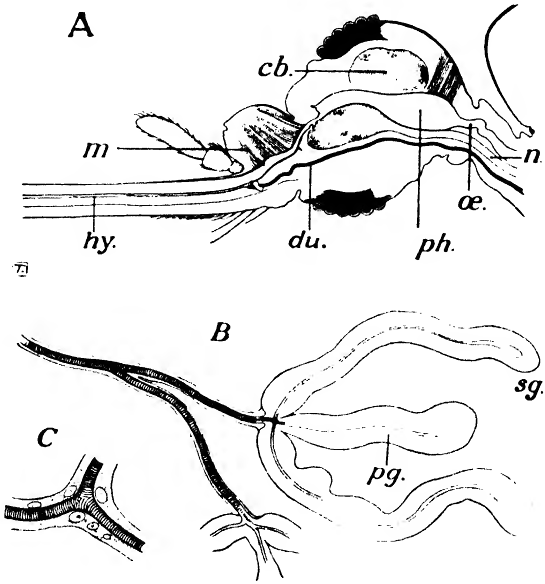


Fig. 208.—Dissection of head of mosquito.

A, Median section of head, showing *du.*, the veneno-salivary duct, with its insertion in *hy.*, the hypopharynx; *cb.*, cerebrum; below this are the cerebellum and the pumping enlargement of *œ.*, the œsophagus; *m.*, muscle; *n.*, nerve-commissure. The other parts have been removed. *B*, The veneno-salivary duct, showing its bifurcation and the three glands on one of its branches; *pg.*, poison gland; *sg.* marks the upper of the two salivary glands. *C*, The bifurcation of the duct with its nucleated hypodermis.

infection rate of *A. maculipennis* have been found by Swellengrebel in Holland. King in America found that in the case of *A. quadrimaculatus*, as the result of twelve months' observation, the infection rate was 0·57 per cent., but that in the case of specimens taken in negro huts it was 4·9 per cent. The mere fact that a particular species can be infected in the laboratory proves little as regards its capabilities of transmitting malaria under natural conditions.

Infection of the mosquito may be of long duration; when once the sporozoites have reached the salivary gland the insect may remain infective for 90 days and a single bite may suffice to convey the disease. In some species, though 50 oöcysts are found in the stomach, full development does not take place. As shown by Wenyon, infected mosquitoes may be chilled and the development of the parasites is merely temporarily arrested.

4. *Sarcosporidia*

These parasites live in the muscular fibres or connective tissue of vertebrates. They are elongate sausage-shaped bodies consisting of a cuticle within which is a series of spaces enclosing a number of falciform spores known as "Rainey's corpuscles." The parasite produces a substance called sarcocystine, which is especially toxic for the rabbit. The cysts, which are visible to the naked eye, are commonly known as Rainey's or as Miescher's tubes; they frequently occur in mammals, but rarely in man, in whom they have been found in the muscles of the heart, larynx and arm. *Sarcocystis tenella* is common in sheep and *S. muris* in mice. The species in man is known as *Sarcocystis meischeriana*. There are several genuine recorded cases. Lindemann (1868) found them in the heart-muscle, Baraban and St. Remy (1894) in the laryngeal muscles, Darling (1909) in the biceps of a negro, while Mainfold in 1924, again discovered them in the human heart.

Protozoa-like yeast cells.—Darling in 1909 first described a condition known as histoplasmosis in Panama, in which a heavy intracellular infection of the lungs with a yeast-like organism—*Histoplasma capsulatum*—was found. This organism when studied by Wenyon has been considered to be a yeast. A case was reported by Watson (1931) in U.S.A. The organisms were uniformly distributed. The port of entry is through the skin or upper respiratory tract. The lesions produced occur in those organs where the reticulo-endothelium or alveolar tissue is present in large amounts. In the early stages of the disease necrosis is prominent, followed by phagocytosis, hyalization and fibrosis. The phagocytes of the lung are largely derived from the histocytes occurring in the alveolar wall. *H. capsulatum* closely resembles *Cryptococcus farciminosus* of the horse.

Moore has reopened this question by describing *Histoplasma* as being composed of two species, *Posadasia pyriformis* and *P. capsulata*. It is characterized by acute specific infection, usually affecting epithelial and endothelial cells of the lungs, liver, and spleen. The cells may be present in the blood-stream and can be cultured, and mycelium, chlamydospores, and multispored asci are formed. Dodd and Tompkins have described a case from Tennessee, U.S.A., in a six-month-old infant. The diagnosis was made by finding the organisms enclosed in the large mononuclear cells in the blood stream.

Cifferi and Redaelli consider that Darling's histoplasmosis is a mycosis of the reticulo-endothelium and may be the cause of *dermatitis exfoliativa* associated with lymphadenitis. In sections the organisms were found as yeast-like bodies enclosed within the phagocytes. All the enlarged lymph-glands contained the parasites (Hansmann and Schenken, U.S.A.).

THE SPIROCHÆTES

Spirochætes are spiral organisms with flexile bodies. In the small slender forms which are parasitic in man it is difficult to make out any accurate details of structure. This is only possible in the larger forms found in the mollucsa. These organisms are now regarded as being nearer to plants than to animals, though formerly, on account of the transmission of the blood-inhabiting species by lice and ticks, they were once regarded as protozoa.

Among the spirochætes of pathological importance which have to be

considered in this work are the *Spirochæta pallida* (Fig. 209, *5*), and the corresponding organism of yaws—*Spirochæta pertenue*. These organisms are small, measuring 5–14 μ in length; they are composed of numerous regular corkscrew-like spirals of an amplitude of 1 μ. The extremities of these organisms are pointed, the spirals wavy and regular. Similar non-pathogenic species are found in the human mouth (*S. dentium*), throat (*S. vincenti*), bronchi (*S. bronchialis*), the organism of the so-called "bronchial spirochæ-

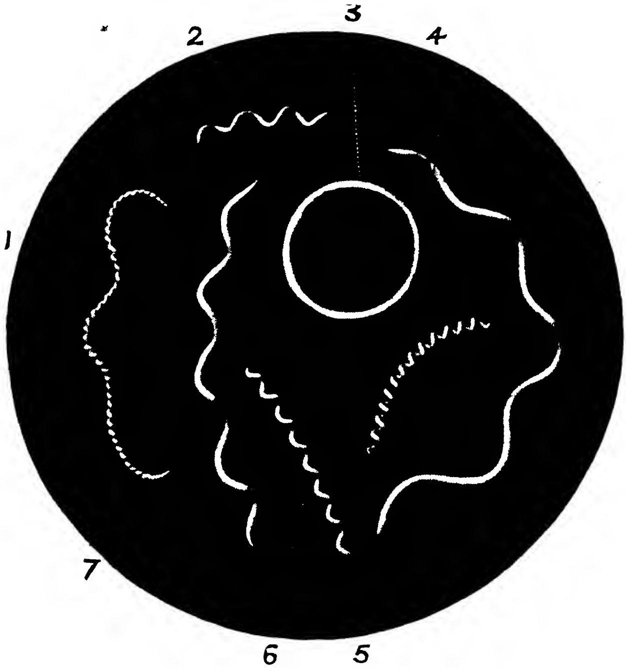


Fig. 209. Schema of different forms of spirochætes. × 3,500.

(*After Dobell; by courtesy of Wellcome Bur. Sci. Res.*)

1. *Leptospira icterohæmorrhagiæ* (Inada and Ido) Noguchi. Cause of spirochætal jaundice.
2. *Spirochæta eurygyratum* Werner. Commonly found in human fæces, both in health and in disease (e.g. dysentery).
3. Human red blood-corpuscle on same scale.
4. *Spirochæta recurrentis* Leber (= *Spirochæta obermeieri* Cohn). Occurs in blood in relapsing fever.
5. *Spirochæta pallida* (Schaudinn) Vuillemin (= *Treponema pallidum* Schaudinn). Syphilis.
6. *Spirochæta gracile* Levaditi and Stanesco. Found on external genitalia, in health and in various diseased conditions.
7. *Spirochæta refringens* Schaudinn (emend.). Occurs in syphilitic lesions on external genitalia.

tosis" (Castellani), intestine (*S. erygyratum*), in tropical ulcers *S. schaudinni*), in ulcerating surfaces (*S. refringens*) and elsewhere.

The larger forms of *Spirochæta* are more flexible and snake-like, and comprise the organisms of relapsing fever (*S. recurrentis*, Fig. 209, *4*, *S. duttoni*, *S. persica*, etc.) in man; and *S. anserinum* and *S. gallinarum*, the cause of spirochætosis in geese and fowls. The human forms are transmitted by ticks (*Ornithodorus*), or lice; those of birds by ticks (*Argas*).

All these organisms progress by a corkscrew action resulting from revolution on the longitudinal axis.

The genus **Leptospira** (Noguchi, 1917), includes the type organism, *Leptospira icterohæmorrhagiæ* (Fig. 209, *1*). These organisms measure 7–14 μ in length, with pointed ends, and a spiral amplitude of 0·45 μ, with one or more gently undulating curves. There is no terminal filament, axial filament or undulating membrane, but very frequently the end is bent in the form of a crook. Two pathogenic species have been recognized—*L. icterohæmorrhagiæ* of Weil's disease and *L. hebdomadis* of seven-day fever.

L. icterohæmorrhagiæ is found commonly in the urinary tract or liver of rats and possibly occurs as a free-living form in water (Zuelzer), while Buchanan has found it in the slime on the roof of a mine in Scotland. The form in rats, like that in man, is highly pathogenic to guinea-pigs. *L. hebdomadis* is found as a natural infection in the field-vole, *Microtus montebelloi.*

Simple division transversely into two, is the usual method of reproduction of spirochætes. No sexual phenomena are known in any spirochæte and the life-histories of all appear to be very simple. Some observers maintain that spirochætes may break up into minute granules (granular phase) which are able to regenerate spirochætes.

The organism of rat-bite fever, formerly known as *Spirochæta morsusmuris* (p. 239), is no longer considered (Robertson, Dobell, etc.) to be a spirochæte, but a spirillum. The correct terminology of this parasite should be *Spirillum minus* (Carter, 1887); synonyms, *Spirochæta laverani* (Breinl and Kinghorn, 1906); *Spirochæta muris* (Wenyon, 1906)

II. MEDICAL HELMINTHOLOGY

TREMATODES, OR FLUKES

These are unsegmented, flattened, leaf-like, or rarely, cylindrical bodies. A mouth is present, and one or more suckers, the posterior of which serves as an organ of attachment, while the anterior is alimentary in function. The intestine is bifurcated, and both branches usually end blindly.

Fasciolopsis buskii (Lankester, 1857)

The parasite lives in the small intestine of man—has even been found in the stomach. In certain parts of China 5 per cent. of the inhabitants are found infected, but only a small percentage of these show characteristic symptoms.

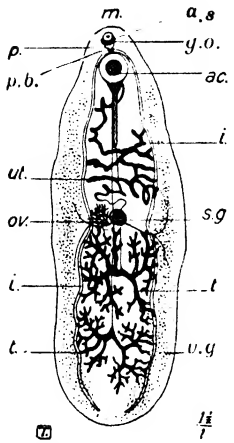


Fig. 210.[1]—*Fasciolopsis buskii.* (*After Odhner.*)

F. buskii is an Asiatic trematode, having been reported from India, Assam, the Straits Settlements, Sumatra, Borneo, and China. The pig is the normal host and acts as the reservoir of the infection in man.

This trematode is the largest which is parasitic in man (Fig. 210). The average length is 30 mm., breadth 12 mm., and thickness 2 mm. It is a thick, flesh-coloured fluke of elongated oval shape, narrower anteriorly than posteriorly. The cuticle on the ventral surface is covered with spines arranged in transverse rows, most numerous in the region of the ventral sucker. The oral sucker (0·5 mm. in diameter) is subterminal and placed on the ventral surface. The ventral sucker is larger (1·6–2·5 mm. in diameter), and placed close to the oral. It is prolonged into a kind of sac (2–8 mm. long) directly under the ventral surface. The pharynx (0·7 mm. long) is preceded by a prepharynx (0·28 mm. long); the œsophagus is very short, and the intestinal cæca are simple and present two characteristic curves towards the middle line, one at about the middle of the body, the other between the testes. The genital pore opens on the median line immediately anterior to the ventral sucker. The testes are in the posterior half of the body, one behind the other; both are branched dichotomously. The ovary is branched, and is placed about the middle of the body on the right of the

[1] The following is a key to the terminology of anatomy of trematodes, as illustrated in this and other figures: *a.s.*, anterior sucker; *m.*, mouth; *p.*, pharynx; *p.b.*, pharyngea bulb; *ac.*, acetabulum or ventral sucker; *g.o.*, genital opening; *ut.*, uterus; *v.g.*, vitelline glands; *ov.*, ovary; *s.g.* shell-gland; *va.*, vagina; *oo.*, oötype; *ovd.*, oviduct; *v.s.*, vesicula seminalis; *r.s.*, receptaculum seminis; *t.*, testis; *v.d.*, vas deferens; *œs.*, œsophagus; *i.*, intestine; *i.c.*, branch intestine *ex.p.*, excretory pore; *n.c.*, nerve cord; *l.c.*, Laurer's canal.

median line. The vitellaria are well developed, and extend from the ventral sucker to the caudal end of the body, where they meet. Their acini are very small. There is a fine tortuous Laurer's canal. The eggs (Plate XXXIII, *1*, facing p. 1025) are numerous, and measure 120–130 μ in length by 77–80 μ in breadth; they are closed by a very delicate operculum.

The evolution of this parasite in a mollusc is in the main similar to that of *F. hepatica*, and was worked out by Nagakawa (1920). After the egg has lain in water for two or three weeks a ciliated miracidium, with two pigmented eyespots and two flame-cells, escapes and enters the body of a snail, a species of Planorbis—*P. cœnosus*, *P. schmackeri*, *P.* (*Segmentina*) *hœmisphærula*, *P.* (*Segmentina*) *largillierti* and *P. nitidella* (Barlow); it then becomes transformed into a sporocyst, within which, in three or four days, rediæ develop, these in turn giving rise to cercariæ. On becoming free in the water, the cercariæ encyst on fresh-water plants, especially the red water calthrop or ling (*Trapa* (*Salvinia*) *natans* in China, *Trapa bicornis* in India) and the water-chestnut (*Eliocharis tuberosus*), which are fertilized with night-soil and are raised in the shallow ponds in which the snails live. In the plant the cercariæ become transformed into *metacercariæ*, which attach themselves to the stems. Raw "ling" (calthrops) is eaten as a vegetable by the Chinese. It is difficult to peel, and man becomes infected in chewing it, as the metacercarial cysts adhere to the teeth and are swallowed. Another water plant which has recently been incriminated is *Spirodela polyrhiza* on the leaves of which the cercariæ encyst.

The cycle, from the entry of the miracidium into the snail till encystment occupies a period of forty-nine days.

Pathogenesis and treatment.—*F. buskii* inhabits the upper part of the small intestine. A few flukes cause no inconvenience beyond slight asthenia and anæmia; when many are present, they cause alternate diarrhœa and constipation; the stools are light yellow and offensive. Œdema involving the face is commonly seen, and may also affect the abdominal wall, genitalia, and lower limbs, and cause ascites. The skin becomes harsh and yellow. Death may occur from exhaustion. It is important to remember that occasionally the abdominal pain produced may resemble that of duodenal ulcer.

The best treatment is to give thymol, beta-naphthol, eucalyptus oil, or carbon tetrachloride as in ancylostomiasis. Recently hexyl-resorcinol has also been found effective. The dose is 0·4 grm. for a child under seven, and 1 grm. from thirteen years upwards.

Fasciola hepatica (Linn., 1758)

The liver fluke has been reported in man as an erratic infection in some fifty instances—in the liver, the portal veins and in subcutaneous abscesses. It is said to occur in the Lebanon as a bucco-pharyngeal infection where it is locally known as "halzoun." In some instances a general cachexia and anæmia resembling that of *diphyllobothrium* anæmia is produced, with an eosinophilia of 54 per cent. Cases of human infection have been noted in Venezuela, Argentina, France, Hungary, Salonika, the Dardanelles and China; usually, however, it seems to cause little disturbance save minor attacks of diarrhœa.

Epileptiform fits have been described by Kouri in Cuba, when the diagnosis was confirmed by the discovery of the eggs in material removed by duodenal sound. Emetine in large doses is said to be effective; for a man of 70 kilos, it should be injected in doses of 6, 5, 5, and 5 cgm. on successive days, with suitable intervals for the elimination of the drug. In one case the amount was 46 cgm., an average of 6·4 mgm. per kilo body-weight.

F. hepatica is a parasite of herbivorous animals, especially sheep, in which it causes the disease known as "liver rot." In colour pale-grey with dark borders; length,

20–30 mm.; breadth, 8–13 mm. The anterior extremity, which bears the oral sucker, is narrow; the posterior, rounded. The ventral sucker is the larger of the two, and is situated 3 mm. from the anterior extremity. Both branches of the intestinal cæca are furnished with many diverticula radiating outwards. The ovary is racemose, and lies in front of the testes, which occupy most of the posterior part of the body.

The uterus lies in front of the ovary, and is short in comparison to the rest of the body; an exsertile cirrus is present. The genital pore is median, half-way between the oral and ventral suckers.

The *eggs* measure 130–145 μ in length by 70–90 μ in breadth; they are ovoid and operculated, and usually of a brown colour due to bile-pigment. The egg, when passed, contains an ovum and yolk-cells.

The life-history of this fluke was first worked out by Thomas and Leuckart in 1883. A ciliated miracidium develops in the egg in about three weeks, and on escaping finds its way into fresh-water snails of the genus *Limnæa*. In Europe the species is *L. truncatula*; in

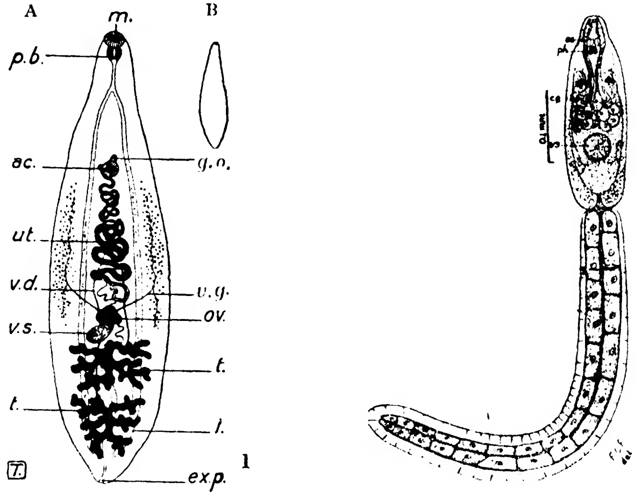


Fig. 211.—(1) Clonorchis sinensis, A, magnified; B, natural size. (*Partly after Looss.*)

(For lettering, *see* p. 894, footnote.)

(2) Cercaria of *Clonorchis sinensis*. (*After Faust and Khaw. By permission of "The American Journal of Hygiene."*)

OS.=oral sucker. PH.=pharynx. CG.=cephalic secretory-gland. VS.=ventral sucker.

Japan *L. pervia*. The resulting cercariæ encyst on blades of grass or watercress and are again eaten by the mammalian host. Large specimens, measuring 75 mm. in length, are called *F. gigantica*, but are probably a variety of *F. hepatica*.

Treatment of human infections with massive doses of magnesium sulphate by the mouth combined with intravenous injections of stibosan has been successful. Apparently also emetine injections have some influence on this parasite.

Clonorchis sinensis (Cobbold, 1875)

This fluke lives in the biliary passages of man, and of dog, cat, pig, rat, mouse, camel and badger. The pancreas and its ducts may be infected; it is rarely found in the duodenum, and never in the gall-bladder (Oppenheim).

C. sinensis (Fig. 211, 1) is a common parasite of man in the Far East. It is a spatulate fluke, tapering anteriorly, and measures 10–20 mm. in length

by 2·5 mm. in breadth, is oblong, narrow, flat, and somewhat pointed anteriorly, reddish in colour, and nearly transparent. The oral sucker (0·6 mm.) is larger than the ventral (0·4 mm.), which is situated between the first and second fourths of the body. The cuticle has no spines. The pharynx is globular and short (Fig. 211, 1, *p.b.*), the œsophagus slender and 0·17 mm. long. The intestinal cæca are simple; the genital pore opens on the middle line immediately in front of the acetabulum. The testes are branched, and situated in the posterior portion of the body, one behind the other. The ovary is trilobate, and its coils are anterior to the genital glands. The vitelline glands are moderately developed, and occupy about the middle third of the body. The eggs are 28–30 μ in length by 15–17 μ in breadth, operculated, almost black, contain a ciliated miracidium (Plate XXXIII, *5*, facing p. 1025), appear to be susceptible to desiccation, and cannot withstand decomposition. According to Nagano the egg does not normally hatch in water, but must be actually ingested by the snail before the miracidium can escape. The eggs are passed into ponds where they can remain viable for five weeks. The miracidium has a very short life in the water, and can only live free for twenty minutes in the intestinal contents of the snail (Vogel, 1934). After piercing the œsophagus of the snail, the miracidium becomes a sporocyst which soon becomes an elongated redia. These rediæ soon burst through the membrane of the sporocyst into the periœsophageal sinus, and then wander tailwards between the interstices of the liver. At this situation cercariæ develop, and finally they break through the space between the upper surface of the body and the shell and emerge into the water. The free cercariæ are very active. From one miracidium one sporocyst develops 20 rediæ, each of which produces 20 cercariæ. Thus one egg gives rise to 400 cercariæ.

Development takes place in *Bithynia* (*Parafossarulus*) *striatula* (Japan, Korea, Formosa, and China), *B. fuchsiana*, and *B. longicornis* (also in China), and *Melania hongkongiensis*. Sporocysts form in two to three weeks, which in turn produce *rediæ*, and the cercariæ, escaping from the snail, encyst in the muscles of certain Japanese fresh-water fish of the family Cyprinidæ, *Pseudorasbora parva*, *Leucogobio güntheri*, and *Carassius auratus*, the last of which is the most important, as it is commonly eaten pickled or incompletely cooked with soy sauce. Faust has shown that some thirty-four species of Cyprinidæ, Gobiidæ and Anabantidæ are susceptible. At first the cercaria (Fig. 211, 2) secretes a viscous fluid that forms an inner true cyst and is afterwards encapsuled by a fibrous layer formed by the tissues of the fish.

The cercariæ in the water reach their fish host within twenty-four to forty-eight hours, and bore their way into its tissues by means of a histolytic secretion. After forty-eight hours they begin to encyst, but full development to adolescercaria can only take place in a suitable host. In certain species, such as *Carassius auratus* and *Eleotris swinhonis*, they are found under the scales, in others in the flesh; so that domestic animals which eat the offal may become heavily infected, while man himself escapes. The capsule of the adolescercaria forms a protection against the action of the gastric juice. The encysted cercariæ (metacercariæ) can withstand a temperature of 50–70° C. for fifteen minutes. The cyst-wall is digested in the stomach, while the metacercariæ escape into the duodenum and attach themselves to the mucosa in the region of the openings of the common bile-duct. The young distomes are provided with spines which soon disappear, and they attain maturity in twenty six days, when the eggs can be found in the fæces of cats, dogs,

rabbits and guinea-pigs fed on infected fish. The important experiments of Faust and Khaw (1925) showed that the succus entericus dissolves the cyst-wall and stimulates the enclosed larva. Only a small proportion reach the bile-ducts, while the remaining 95 per cent. are digested and destroyed. The metacercariæ, after eleven to twelve days, reach the middle bile-ducts by positive chemotaxis. The size of the fluke is dependent on the stature of its host, and the diameter of the bile-ducts. The egg-production of this fluke is very large. In infected cats it is estimated at 2,400 a day, and 1,125 in dogs. Sambuc and Beaujean (1913) recorded finding 21,000 adult flukes at the autopsy of an Annamese soldier. Men are more often infected than women.

It has been estimated that the life span of the sexually mature flukes is at least twelve years. For pathogenesis, *see* p. 800.

The following is a list (Walker) of the most important snails which may act as intermediaries :

Fossarulus stachei.
F. loczy.
F. sinensis.
Parafossarulus striatulus.
P. striatulus var. *japonicus.*
P. sinensis.
P. subangulatus.
P. woodi.
Pseudovivipara hypocrites.
Hydrobiodes dautzenbergi.
H. nassa.
Bithynia longicornis.
B. moreletania.
B. pœteli.
B. misella.
B. umbilicaris.
B. morleti.
B. goniomphalos.
B. thatkeana.
B. robusta.
B. robusta minor.
B. truncata.
B. dautzenbergiana.
B. siamensis.
B. funiculata.
B. fuchsiana.
B. delavayana.
B. toucheana.
B. lævis.
Melania hainanensis
M. hongkongiensis.

The following is a list of edible fishes which may act as second intermediaries :

Hemiculter kneri.
Acanthorhodeus atranalis.
A. gracilis.
Carassius auratus.
Pseudogobio rivularis.
P. sinensis.
Pseudorasbora parva.
P. fowleri.
Eleotris swinhonis.
E. potamophila.
Paracheilognathus rhombea.
Rhodeus sinesis.
Culter brevicauda.
Sacrocheilichthys nigripinnis.
S. sinensis.
S. morii.
S. variegatus.
Macropodus opercularis.
Biwia zezera.
Xenocyprus davidi.
Pseudiperilampus typus.
Abbotina psegma.
Leucogobio guentheri.
L. striatus.
L. coreanus.
L. mayedæ.
Ctenopharyngodon idellus.
Acheilognathus lanceolata.
A. limbata.
A. cyanostigma.
Labeo jordani.
Hypothalmichthys nobilis.

OPISTHORCHIS FELINEUS (Rivolta, 1884)

The normal hosts of this species are the dog, cat, glutton and pig. It occurs quite commonly in man in East Prussia, Siberia, Annam, and the Philippines.

This lanceolate fluke measures 8–11 mm. in length by 1·5–2 mm. in breadth. The cuticle is smooth, the suckers are of equal size, and separateds from each other by one-fourth of the body-length. (Fig. 212.) The eggs are small, yellowish-brown; 30 μ long by 12 μ broad (Plate XXXIII, 4, facing p. 1030).

According to H. Vogel, who in East Prussia has worked out the life-history in detail, the only snail which acts as the first intermediary is *Bithynia leachi* (Shepp). The miracidium is fully formed in the egg, and is hatched by the osmotic pressure in the alimentary canal of the snail and not by water. The sporocyst develops close to the end of the intestine, and in one month reaches a length of 1·2 to 1·85 mm. and the rediæ are formed. Next the immature cercariæ leave the rediæ, and reach maturity about two months from the date of infection. The cercariæ leave the snail only during daylight. They are shaped like a tobacco-pipe with a tail membrane, and are attracted by light and activated by agitation. The second intermediary hosts are the tench (*Tinca tinca*) and the chub (*Idus melanotus*). The cercariæ penetrate within fifteen minutes, and become metacercariæ, which grow to three to four times the original size. When the fish is eaten, the cysts pass into the stomach unchanged, but are freed by the juice of the small intestine. Bile attracts the young flukes, and they travel up the bile-duct into the liver within five hours.

The infection is contracted by man through eating raw fish. This species does not appear to be specially pathogenic to man, although 200 or more have been found in the liver and bile-ducts at two autopsies.

Two other species of the genus *Opisthorchis* have been recorded in man, but are of no importance—*O. noverca* and *O. viverrini*, the former from India, the latter from Siam. The normal host of *O. noverca* is the dog, that of *O. viverrini* is the civet cat.

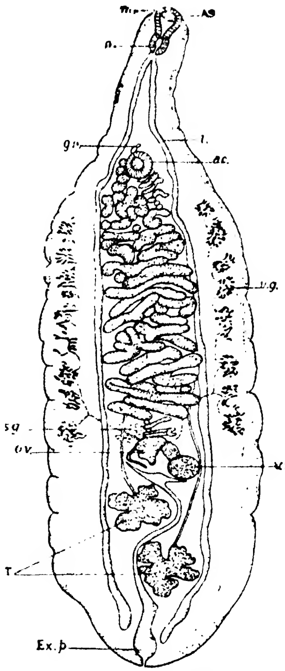


Fig. 212.—*Opisthorchis felineus*. × 9. (*After Barker, in "Archiv de Parasitologie."*) (For lettering, *see* p. 894, footnote.

HETEROPHYES HETEROPHYES (Siebold, 1852)

This species inhabits the small intestine, often in very large numbers, and may cause diarrhœa. *H. heterophyes*, described in 1851 by Bilharz in Cairo, probably has a wide distribution, and has been reported from Egypt, China, and Japan. Under natural conditions it infests the fox, dog, wolf and cat.

H. heterophyes (Fig. 213) is a minute pyriform fluke and measures 1–1·7 mm. in length by 0·3–0·7 mm. in breadth. It has an oval, elongate shape, and when passed and fresh is grey, the uterus showing up as a brown patch in the centre of the body. The oral sucker (0·09 mm. in diameter) is subterminal, and about one-third the size of the ventral sucker (0·23 mm.), which is placed at about the middle of the body. The cuticle is thickly set with quadrate scales, 5–6 μ long by 4 μ broad. The prepharynx is short (80 μ in length); the pharynx measures 50–70 μ in length by 40–50 μ in diameter. The œsophagus is about three times as long. The intestinal cæca extend to the posterior extremity, where they converge and terminate close to the excretory vesicle. The vitelline glands are arranged in two clumps at the posterior end of the body. The genital pore opens postero-laterally to, and in the immediate vicinity of, the ventral sucker; it is surrounded by a muscular

ring, and is armed with about 70 antler spines. The testes are oval, and situated posteriorly. The ovary is globular, median, and anterior to the testes. The receptaculum seminis is as large as the ovary; the uterine coils are not numerous, and extend between the ventral suckers and the testes. The eggs are light-brown, thick-shelled, oval, 20–30 μ by 15–17 μ, and contain a ciliated embryo when oviposited. (Plate XXXIII, 3, facing p. 1030.)

Life-history.—The mollusc which acts as the first intermediary is unknown, but the cercaria is apparently an oculate lophocerca known as *C. pleurolophocerca* (Sonsino), and which is found in Egypt in *Melanoides tuberculatus* and in *Cleopatra bulimnoides*. Onji and Nishio, and Khalil in Egypt, have found that infection is acquired from eating raw mullet (*Mugil cephalus*). Khalil has now discovered that the common snail host in

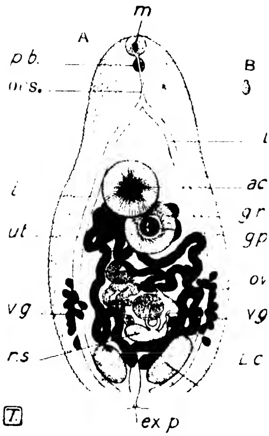


Fig. 213.—*Heterophyes heterophyes.*

A, Greatly magnified; B, natural size.

(For lettering, *see* p. 894, footnote.)

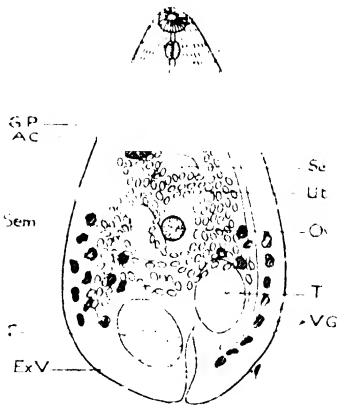


Fig. 214.—*Metagonimus yokogawai.* × 45. (*Partly after Leiper.*)

Sem. Ves., seminal vesicle; Rec. Sem., Receptaculum seminis; G.P., genital pore. (For other lettering, *see* p. 894, footnote.)

Lake Manzala, Egypt, is a conical snail, *Pirenella conica*, and that the metacercariæ can also encyst on a minnow, *Gambusia affinis*. Africa, Garcia and de Leon, in nine autopsies in Manila, found heterophyid eggs in the walls of the intestines, as well as in the muscles of the heart, which produced symptoms during life resembling those of cardiac beriberi. They recognize two new human species of *Heterophyes*, namely, *H. brevicæca* and *H. taihokui*.

Treatment.—The adult flukes are removed from the intestines by means of thymol (p. 813) and also by oleoresin of aspidium (p. 822).

METAGONIMUS YOKOGAWAI (Katsurada, 1912)

Synonym.—*Loxotrema ovatum.*

Yokogawa's fluke occurs commonly in the small intestine of natives of Korea, Formosa, Japan, and the Balkan States; it is also common in cats, dogs, pigs, and the pelican (*Pelicanus onocrotalus*).

This is the commonest intestinal fluke of the Far East. It measures

only 1·1 mm. long by 0·42–0·7 mm. broad; the cuticle is covered with small spines; it is the smallest fluke which occurs in man.

It differs from other members of this class in having the ventral sucker, or acetabulum, displaced somewhat laterally on the left side. The common genital pore lies immediately in front of the ventral sucker. (Fig. 214.) The testes are ovoid and are situated in the posterior third of the body. The ovary and the receptaculum seminis lie immediately in front of the testes in the midline. The yolk-glands are arranged in clumps in the posterior third of the body, and the uterus occupies the space which lies between the testes and the ventral sucker. A large seminal vesicle is present, and lies immediately in front of the ovary. The egg resembles that of *Clonorchis sinensis* in size, but is more regularly ovoid in shape (*see* Plate XXXIII, *6*, facing p. 1030); it measures 33 μ in length by 21 μ in breadth.

There are two intermediary hosts—a fresh-water snail, *Melania libertina*, or *M. ebenina*, in which the redial and cercarial stages occur, and a fresh-water fish, *Plectoglossus altivelis*, under the scales of which the metacercariæ have been found to encyst. On entering the fish the tail is discarded. The anterior end of the cercaria is provided with a peculiar armament, which serves to distinguish it from opisthorchid larvæ. The tail is long and lophocercous with lateral flutings.

The fish is often eaten in a raw state by the Japanese. In some districts of Japan 50 per cent. of the snails are infected with the cercariæ of this parasite.

Pathogenesis.—*M. yokogawai* is an apparently innocuous parasite in man, causing at the most a catarrhal condition of the intestinal tract which it inhabits.

Paragonimus ringeri (Cobbold, 1880), and Allied Species: P. westermanii and P. compactus

P. ringeri would seem to be confined to Japan and Korea. In man, the dog, fox, wolf, panther and cat, it is found in the lungs.

P. ringeri (Fig. 215) is oval in shape, reddish-brown in colour, and somewhat translucent; so thick is it that it is almost round in transverse section. It measures 8–20 mm. in length by 5–9 mm. in breadth. The anterior extremity is bluntly rounded, without a cephalic cone. The oral sucker (0·88–1·12 by 0·80–0·83 mm.) is terminal or subterminal. The ventral sucker, slightly larger than the oral, is situated somewhat anteriorly to the middle of the body. The pharynx is present and the œsophagus is short, so that the bifurcation of the intestine is considerably anterior to the ventral sucker. The intestinal cæca run a zigzag course towards the caudal end of the body. The common genital pore opens close to the posterior margin of the ventral sucker. The whole of the body is divided into two halves by the large excretory vesicle which lies in the long axis. The testes are tubular racemose glands, and are situated on each side of the middle line in the posterior third of the body. The ovary is branched, and may lie either to the right or the left of the midline, just posterior to the ventral sucker. The uterus is short and somewhat sac-like, and lies opposite to the ovary on the other side of the body. The vitellaria are greatly developed, and extend throughout the whole length of the body. Laurer's canal and a large shell-gland are present. The cuticle is studded with groups of wedge-shaped

spines; these groups may vary in number from three to twelve, according to their position. The spines are the only reliable structures by which this can be differentiated from the closely-allied species which occur in man—namely, *P. westermanii*, in which the spines are arranged singly, and *P. compactus*, in which they are arranged in clumps—but they are fewer in number, pointed, and not wedge-shaped as in *P. ringeri.*

The egg of *P. ringeri* measures, on an average, 90 μ in length by 55 μ in breadth. It is operculate, brown in colour, and there is a slight thickening at the opposite pole to the operculum. (Plate XXXIII, facing p. 1030.)

The egg of *P. westermanii* is slightly smaller, and measures 85 μ in length by 55 μ in breadth, while that of *P. compactus* is smaller still, and measures

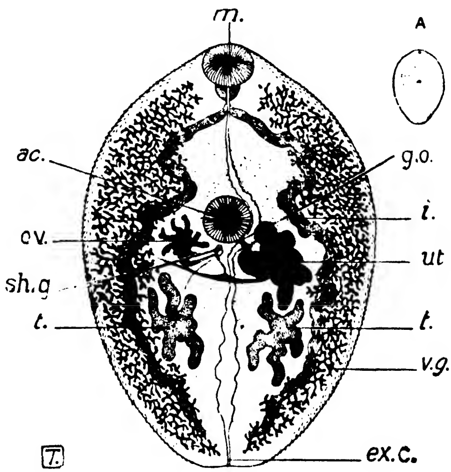


Fig. 215.—*Paragonimus ringeri.* (*Partly after Looss.*)
A, Nat. size. (For lettering, *see* p. 894, footnote.)

75 μ in length, and on an average 48 μ in breadth. Neither of these eggs has so marked a thickening at the opposite pole to the operculum as has the egg of *P. ringeri.*

The **geographical distribution** of these three species is also somewhat different. *P. ringeri* would seem to be confined to Japan and Korea, French Indo-China, Philippines, and Siam, whereas in India and in the Malay States man is liable to be infected with *P. compactus* and *P. westermanii.* A fourth species occurs in the pig, dog, and cat in North and South America, and in the tiger in the Malay States; it is known as *P. kellicotti*, and up to the present has not been recorded from man.

Life-history (Fig. 216).—The eggs of *Paragonimus* are broadly oval with a distinct operculum and a thickening of the shell at the opposite end. They are voided into cystic pockets in the lung around the flukes, and escape in the sputum when these pockets rupture. On reaching water the eggs hatch in four to seven weeks and the miracidium enters a fresh-water snail of the genus *Melania.* According to Watanabe the miracidium has the following distinctive characters: The ciliated covering is made up of 17 cells

arranged in four rows, the numbers in each row being 6, 7, 3 and 1; there is an anterior cone, no eye-spots, and a pair of sense organs, while the excretory canal forms a rosette. At least six species of *Melania* have been found to serve as intermediary hosts, including *Melania tuberculata* (Japan and China), *M. libertina* (Japan. China and Korea), *M. obliquegranulosa* (Formosa), M. *paucicincta*, *M. gottschei*, *M. extensa*, and *M. nodiperda* (Korea). Therein the miracidium undergoes the usual developmental changes of sporocyst and redia, eventuating in the formation of cercariæ. In Venezuela (in the case of *P. kellicotti*) the snail is said to be *Ampullaria luteosoma*. The cercariæ are microcercous with an ellipsoidal body and a knob-like tail, measuring from 200 μ in length by 70–80 μ in breadth. The cercariæ in due time escape into the water and bore their way by means of the stylet into certain species of fresh-water crustacea—*Potamon obtusipes*, *P. dehaani* (Fig. 217), *P. sinensis*, *Sesarma dehaani*, *A. dahionicus*, *Eriocheir japonicus* (Fig. 218), *Astacus japonicus*, and in Korea, *Eriocheir sinensis* and a crayfish, *Cambaroides similis*.

Fig. 216.—Life-history of *Paragonimus ringeri*. Figs. 3-9, × 15. (*After Nakagawa, " Journ. Exp. Med."*)

1, 2, First intermediary hosts, *Melania libertina* and *M. obliquegranulosa*, quarter nat. size; 3, 4, cercaria and sporocyst of *P. ringeri*, in *Melania*; 5, 6, 7, tailless cercaria and encysted cercaria in liver of crab as second intermediary host; 8, fully-grown encysted metacercaria; 9, adolescent paragonimus, 14 days old.

In Venezuela the species is *Pseudothelphusea iturbei*. In these the cercariæ encyst themselves in the liver, muscles, etc., and especially in the gills. In Japan, man is commonly infected by eating the raw flesh of crustacea. In Korea and Formosa, however, where paragonomiasis is very common, uncooked crabs are not eaten. One is therefore led to suppose that encystment in the crustacean is not a biological necessity for the parasite; it may be that the cercariæ gain their entrance to the body in some other vehicle, such as drinking-water. On entering the stomach, the cyst is digested out and the *adolescercaria* emerges, traverses the abdominal cavity, penetrates the pleura and lungs, and finally arrives in the bronchioles, where it settles down in a cystic cavity.

Pathogenesis is fully detailed at p. 796.

Other members of the Trematoda have been recorded from man, but are of such infrequent occurrence as to be of little practical importance to the student of Tropical Medicine ; these are—*Dicrocœlium lanceatum*, of which

Fig. 217.—*Potamon dehaani.* Half nat. size

Fig. 218.—*Eriocheir japonicum*, ♂. Quarter nat. size.

the normal host is the sheep ; *Echinostomum malayanum* of the pig, from the Malay States ; *Artyfectinostomum sufartyfex* (which is probably identical with *E. malayanum*), from Assam, and *E. ilocanum*, from the Philippines.

THE BILHARZIA GROUP

Bilharzia hæmatobia (Meckel, 1856)

Synonym.—*Schistosoma hæmatobium* (Weinland, 1858).

This parasite (Fig. 219) is found in the venous system of man, especially the mesenteric branches of the portal vein, the vesico-prostatic, the pubic and uterine plexuses, and the vesical veins ; occasionally it may wander into the vena cava and into the pulmonary veins. As many as 300 have been found at autopsy, and in experimentally-infected monkeys they may

be even more numerous; they appear to be especially abundant in the veins of the submucosa of the bladder.

The parasite can, under experimental conditions, be conveyed to a number of animals—rats, mice, guinea-pigs, monkeys, and hedgehogs (Brumpt).

B. hæmatobia is confined for the most part to the continent of Africa. Endemic foci also exist in Cyprus, Corsica, Palestine, Morocco, Algeria, Tunis, Arabia, Madagascar, Mauritius, Réunion, and Iraq. It is recorded that after the South African War the infection was imported into Perth, Western Australia.

The adult parasite is long-lived. The Editor has seen active cases of the disease of twenty years' standing, and others, e.g. Christopherson, have recorded still longer periods. The sexes live apart while young, but on reaching maturity the female enters the *gynæcophoric canal* of the male.

In both sexes the alimentary canal commences at the oral sucker, the ventral sucker, or acetabulum, being prehensile in function. The œsophagus presents two dilatations, and bifurcates just in front of the ventral sucker to form two intestinal cæca, which again unite about the centre of the body into a median trunk. The excretory system consists of two longitudinal canals which open posteriorly and somewhat dorsally by the excretory pore.

The nervous system is represented by an œsophageal ganglion and commissure, embracing the œsophagus, from which the longitudinal nerve-cords run to the posterior end of the body; these cords intercommunicate by means of lateral branches.

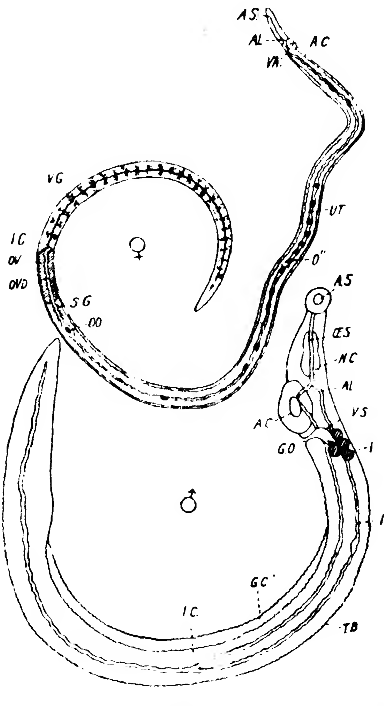


Fig. 219.—*Bilharzia hæmatobia.* 10. (*Orig.*)

C., Ventral sucker; AL., bifurcation of alimentary canal; A.S., anterior sucker; G.C., gynæcophoric canal; G.O., genital opening; I., intestine; I.C., union of intestinal cæca; N.C., nerve cord; O", terminal-spined ovum; ŒS., œsophagus; OO., oötype; OV., ovary; OVD., oviduct; S.G., shell-gland; T., testes; T.B., tuberculations; UT., uterus; VA., vagina; V.G., vitelline glands V.S., vesicula seminalis.

The **male** is white, cylindroid, 1 to 1·5 cm. in length by 1 mm. in breadth, and it possesses an oral and a ventral sucker (of which the latter is the larger) placed close together. The oral sucker has the dorsal lip longer than the ventral. The cylindrical appearance of the worm is produced by the ventral infolding of the two sides of what would otherwise be a flat body. By this infolding a gynæcophoric canal is formed, in which the female can be partially enclosed. The outer surface of the body is closely beset with small cuticular prominences, especially on the dorsal surface. There are delicate spines on the suckers, and large tuberculations on the inner surface of the gynæcophoric canal.

The reproductive system consists of 4 to 5 testes, round in shape, and lying posterior and dorsal to the ventral sucker; from these a similar number of vasa efferentia unite to form a long vesicula seminalis, to open at the genital pore, in the median line, just posterior to the ventral sucker.

The **female** is rather darker in colour than the male, considerably longer (2 cm. by 0·25 mm. in breadth), and filiform; her middle portion is usually infolded in the gynæcophoric canal of the male, while her anterior and posterior portions remain free. Her body is smooth, except towards the posterior end and on the suckers, where papillæ abound. The reproductive system consists of an elongated oval ovary lying in the posterior half, in front of the union of the intestinal cæca. From the posterior pole of the ovary arises the oviduct, which on passing forwards is joined by the vitelline duct. The yolk-glands, or vitellaria, occupy the posterior part of the body. The shell-gland opens into the oviduct, which on passing forwards becomes the uterus. The genital opening is median, and situated just posterior to the ventral

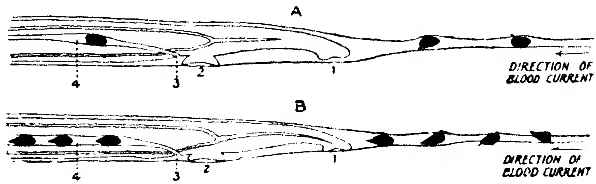


Fig. 220.—Diagram representing deposition of eggs by (A) *B. mansoni* **and** (B) *B. hæmatobia* **in blood-vessels, and their passage to exterior.** (*Orig.*)

1, Anterior sucker; 2, posterior sucker; 3, vaginal orifice; 4, uterus with contained eggs.

sucker. The anterior portion of the uterus contains several terminal-spined eggs. The genital openings of the sexes face each other, and are placed immediately posterior to the ventral sucker.

On microscopical examination, the uterus of the female is found to contain 20–30 eggs of a peculiar and characteristic shape. They are oval, each egg on an average measuring about 150 μ in length by 60 μ in breadth. One end of the egg is provided with a short, stout, and very definite spine. (Plate XXXIII, *11*, facing p. 1030.)

The exact nature of the process by which the eggs leave the body of the human host has been explained by Fairley and the Editor from observations upon experimentally-infected monkeys whose mesentery had been exposed under anæsthesia. The paired worms travel against the blood-stream to the furthermost possible point, where the female leaves her partner, and, being of a smaller diameter, is able by means of her suckers to progress until she stretches the smaller venules to their uttermost. The eggs are now deposited with their spines directed posteriorly. The female then withdraws so that the egg she has deposited lies a little in front of the anterior sucker. The process is then repeated. When, after the deposition of an egg, the worm retires, the vein contracts to its original dimensions, embracing the egg, and the returning blood drives the spine into the wall of the vein. (Fig. 220.)

In a large proportion of cases, much more frequently than was formerly thought to be the case, the characteristic eggs of *B. hæmatobia* may be found in the fæces (*see* p. 720) Chesterman has reported from the Congo a much-elongated variety of terminal-spined egg which occurs in the fæces only, and not in the urine, and which has now been referred to a separate

species—*B. intercalata.* Eggs of *B. hæmatobia* are not uncommonly found in the lungs, occasionally in the brain and other atypical situations.

In newly-voided urine the egg presents a somewhat brownish appearance, and generally contains a ciliated embryo (Fig. 221), which escapes through a transverse rupture in the shell, caused by osmosis on coming into contact with water, and by a digestive ferment elaborated by the miracidium. It then swims about, but, unless supplied with fresh water, perishes within a period of twenty-four hours. While swimming, the body of the miracidium undergoes many changes of shape. It moves by means of the cilia which, with the exception of the minute papillary beak, thickly cover the entire body. On careful examination, a primitive intestine may be traced from the anterior papilla; on each side of this, two unicellular salivary, or cephalic, glands can be made out, with ducts opening into the mouth. The bulk of the embryo is occupied by a number of germ-cells, the posterior part by excretory tubules connected with four large flame-cells. The nervous system is represented by an oval, irregular mass lying in the centre of the body. According to Leiper and Ashworth's observations, the cuticle of the miracidium is composed of a number of polygonal epithelial cells. The body is divided transversely into three zones, united by six or seven longitudinal strands.

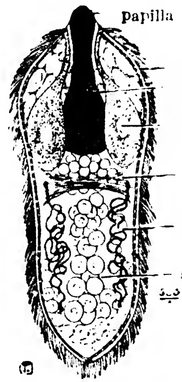


Fig. 221.—*B. hæmatobia* **miracidium.** (*After Looss.*)

According to Dye, the miracidia of *B. hæmatobia* hatch more rapidly and travel farther before entering their intermediate host than do those of *B. mansoni.*

The miracidium is attracted by the appropriate species of mollusc, usually of the genus *Bullinus.*

The miracidium penetrates the soft part of the mollusc, usually boring its way through the antennæ. The cilia are then cast off; travelling *via* the lymph spaces and the interhepatic lymph sinuses, it comes to rest in the liver or digestive gland. There the miracidium develops into an elongated sac-like body called a sporocyst, in the interior of which daughter-sporocysts form. These latter multiply to such an extent that the entire liver becomes permeated with the long, delicate, transparent, tube-like bodies. Presently numerous bifid-tailed cercariæ develop within the sporocysts and, on maturing, escape spontaneously into the surrounding water. The cycle from miracidium to cercaria under suitable conditions of temperature takes fourteen days to complete. Opportunity occurring, the now free cercariæ penetrate the skin of some suitable vertebrate—man, mouse, rat, monkey—dropping their tails in the process (Fig. 229, p. 915). Entering lymphatics or blood-vessels, they proceed to the liver of the definitive host, and in about six weeks attain sexual maturity and produce terminal-spined eggs. To obtain these results in the laboratory, all that is necessary is to place the living experimental vertebrate, or a part—tail, limb, etc.—of such animal, in water into which cercariæ have escaped from the snail, care being taken that the dose of cercariæ is not too large, as in such case the excessive invasion of the liver may prove rapidly fatal. In man, as well as in experimental animals, the presence of

numerous examples of this parasite in the liver causes a heavy deposition of dark pigment (hæmatoidin) in the interstitial cells.

The intermediary hosts of this species are *Bullinus contortus* (Egypt), *B. dybowski* (Egypt), *B. innesi* (Egypt and Sudan), *B. truncatus* (Palestine), *B. forskali* (Mauritius and Kenya), *B. globosus* (Sierra Leone and Nyasaland), *B. africanus* (Natal), *Isodora ovoidea* (Zanzibar), *Planorbis corneus* var. *metidjensis* (Portugal).

Fresh-water snails of the genus *Bullinus* have distinctive characters, and the opening of the shell is sinistral (Fig. 222). Annandale considers that all three species, *B. contortus*, *dybowski*, and *innesi*, are really varieties of *Bullinus*

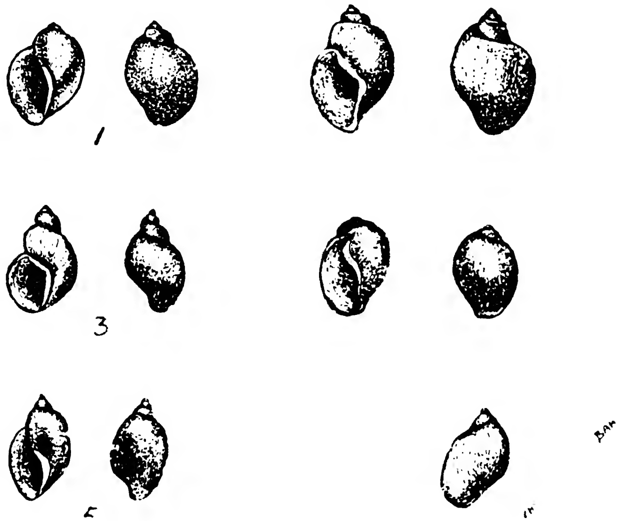


Fig. 222.—Fresh-water molluscs. Nat. size. (*Orig.*)
1. *Bullinus contortus*; 2, *B. dybowski*; 3, *B. innesi*; 4, *B. africanus*—all intermediary hosts of *B. hæmatobia*; 5, *Physa subopaca*, a sinistral snail apt to be mistaken for *Bullinus*; 6, *Limnæa laurenti*, a dextral snail.

truncatus (Audouin, 1809), of which *Bullinus contortus* (Michaud, 1831), (Fig. 222) is a synonym. The synonym of *B. africanus* is *Physopsis africana*)

Bilharzia intercalata

Synonym.—*Schistosoma intercalatum*.

A. C. Fisher has described this new species of Bilharzia from the Upper Congo (Yakusu). The species resembles *B. hæmatobia* and may be described as being half-way between this species and *B. bovis*, but none of the morphological characteristics, apart from the egg, are such as enable it to be clearly differentiated.

The **male** is 1·1–1·4 cm. in length by 0·3–0·4 mm. in breadth. The well-marked gynæcophoric canal extends from behind the ventral sucker to the tip of the posterior extremity. The cuticle is smooth as far back as the commencement of the gynæcophoric canal, and the rest of the body is covered with tubercles. Fine spines cover the tubercles. The alimentary canal resembles that of *B. hæmatobia*. The genitalia are characterized by a testicular mass composed of an average number of four testes. The **female** measures 1–1·4 cm. in length by 0·15–0·18 mm. in breadth. The cuticle is smooth. The arrangement of the genitalia and of the alimentary canal resemble those of *B. hæmatobia*.

The **eggs** differ considerably. In size the intra-uterine egg averages 130 μ by 40 μ, whilst the measurements of the mature egg in the fæces of man and experimental animals are

140–240 μ in length by 50–85 μ in breadth. In shape they are distinctive. There are two extreme types; on the one hand eggs of the short variety may be confused with those of *hæmatobia*; on the other the long spindle-shaped eggs may resemble those of *B. mattheei* or *B. bovis*, but these never reach such large dimensions (Fig. 223). Van den Bergh and others have thrown doubts upon the specificity of these eggs as distinct from those of *B. hæmatobia*. There is great variation in size in the eggs of this species found in the urine of natives in the Kantanga province of the Congo. The spine of *B. intercalata* ovum may measure 20 μ. "Spinster" females are a characteristic of this species. They lead an independent existence presenting deviations from the normal. They are found when male worms are absent and also when they occur in smaller numbers. Their length is much shorter—5–7 mm. by 0·15 mm.

The snail intermediate host is thought to be *Bullinus africanus* (*Physopsis africana*), which shows a definite seasonal variation in its distribution from December to April, when the water is high and the snail is very widely distributed. When the river falls in May the conditions for the snail become unsuitable, and it appears that the main foci of infection are the local bays or harbours on the Upper Congo. The snail prefers stretches of shallow calm water containing decaying vegetation. In June and July, 2–3 per cent. of the snails give off bilharzia cercariæ.

The adult bilharzia worms described by Fisher were obtained by immersing the tails of mice in cercaria-infected water. A male sheep was also successfully infected *per os*. The shortest period observed between exposure and the appearance of eggs in the fæces of mice was forty-one days. The bilharzia worms were found (as many as 118 pairs in copula) evenly distributed throughout the portal system. The gravid females were never seen apart from the male even when engaged in oviposition. Unisexual infestations were encountered.

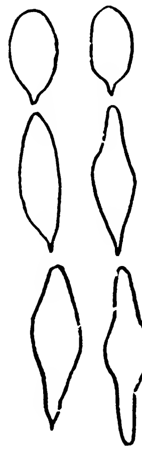


Fig. 223.— Outline drawings of eggs of (A) *B. hæmatobia*; (B) *B. intercalata*; (C) *B. bovis*. (*After A.C. Fisher.*)

Drawn to scale.

Bilharzia mansoni (Sambon, 1907)

Synonym.—*Schistosoma mansoni.*

In man the habitat of this trematode is the inferior and superior mesenteric veins, the hæmorrhoidal plexus, and the portal system. The bilharzia may best be obtained at autopsy by squeezing out all the venous blood from the liver against the side of a glass vessel, when they will adhere to the side of the glass, and can be picked off.

This fluke is generally distributed throughout Africa, being abundant in Egypt, the Congo, and West Africa. In East Africa it is found from Zanzibar to the Zambesi and inland through Northern Rhodesia and Tanganyika. It has been recorded from Kenya, Uganda, Madagascar, Natal, and the Transvaal. It is common in the South American continent—in Brazil, Venezuela, and Dutch Guiana, and in the Antilles, especially Antigua. It is thought that the extension of rectal bilharziasis to the New World was due to the exportation of slaves from West Africa. Cameron has found that the introduced West African green monkey (*Cercopithecus sabæus*) acts as a reservoir of this infection in St. Kitts.

Male.—Length, 1–1·2 cm. The body behind the ventral sucker is clothed with wart-like tuberculations considerably larger and more pronounced than in *B. hæmatobia* (Fig. 122, p. 730). The intestinal canal bifurcates at the level of the ventral sucker, but the intestinal cæca unite early in the anterior half of the body to form a long, single intestinal tract. The genital system consists of eight or nine small testes, with as many vasa efferentia opening into the vesicula seminalis. (Fig. 224.)

Female.—Length, 1·2–1·6 cm. As in the male, the intestinal cæca unite in the anterior half of the worm.

The ovary lies in the anterior half of the body, in front of the union of the intestinal cæca, and in consequence the uterus is very short and contains a few lateral-spined eggs, or more generally one, with spine directed posteriorly. The yolk-glands occupy about two-thirds of the body at its posterior end. The eggs (Plate XXXIII, *21*, facing p. 1030) are 150 μ long by 60 μ in breadth, on the average; the lateral spine itself measures 20 μ. Those obtained from the intestinal lesions differ considerably from the fully matured specimens in the fæces.

The eggs are deposited by the female in the subterminal branches of the mesenteric veins, in the same manner as those of *B. hæmatobia*, and probably the lateral spine aids in forcing the way through the tissues into the lumen of the bowel. Faust and Hofmann found that some eggs pass through the

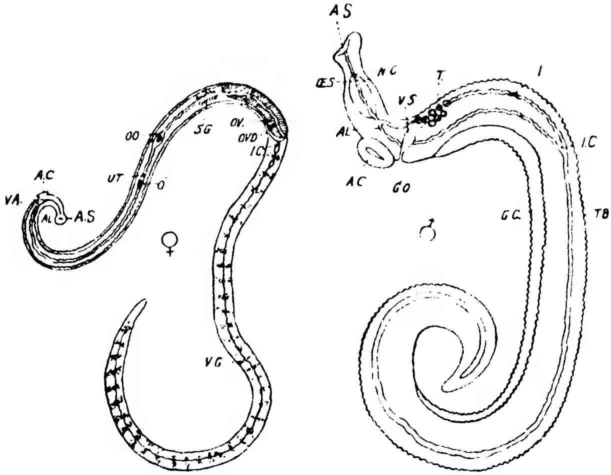


Fig. 224.—*Bilharzia mansoni.* × 10. (*Orig.*)
(For lettering, *see* inscription to Fig. 219; *o′*, lateral-spined egg.)

muscularis mucosæ of the bowel-wall into the glands of the mucosa via the capillaries; others break out of the vessels into the submucosa and work their way through the substance of the tissues, or lodge in the submucosa and become the centres of infiltration.

The miracidium is very similar to that of *B. hæmatobia*, but is said to be larger.

Except that the species of intermediary host concerned are different development is identical with that of *B. hæmatobia* (p. 907). In the space of 10–15 minutes the miracidium penetrates into the tentacles of the mollusc, and produces thereby a swelling by which infected snails can be recognized. Within three or four days the miracidium becomes a sporocyst, which on the fifth or sixth day gives rise to daughter-sporocysts, and these in turn migrate on the twentieth day to the liver. The cercariæ themselves are produced by the daughter-sporocysts (Leiper).

The cercaria was formerly thought to differ in measurements from that of *B. hæmatobia*, but this has not been substantiated.

After penetration of the host the trematodes take about six weeks to reach maturity. The females lay their eggs in the portal system, and eventually they are excreted by passing through the intestinal mucosa into the fæces, and by this means escape to the exterior.

Should the fæces be diarrhœic, the escape of the miracidium from the egg may even take place in the lumen of the bowel. The miracidia are attracted by light, and are thereby enabled to disentangle themselves from the meshes of the fæces.

In most countries the intermediary host of *B. mansoni* is a mollusc of

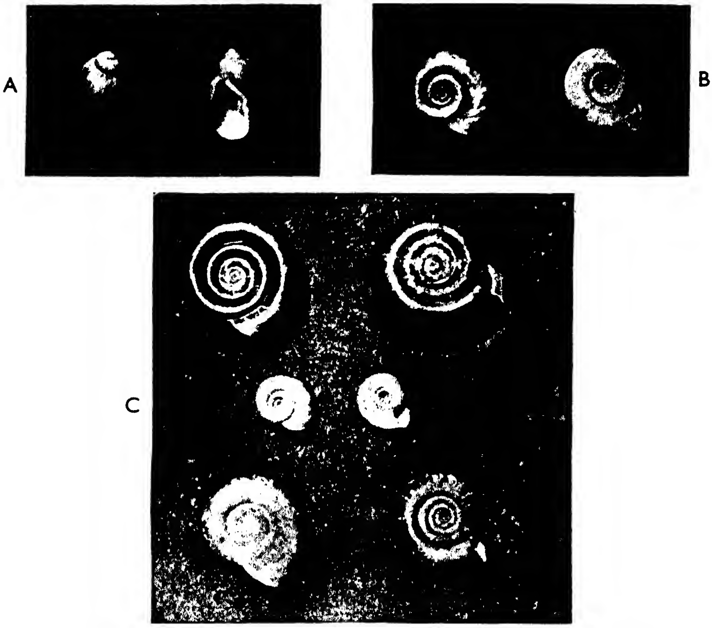


Fig. 225.—Carriers of *Bilharzia hæmatobia* and of *B. mansoni* in Egypt, South America, and West Indies. (*After Leiper.*)

A, *Bullinus contortus* (nat. size). B, *Planorbis boissyi* (nat. size). C, *P. olivaceus*; *P. boissyi*; *P. guadeloupensis* (two-thirds nat. size).

the germs *Planorbis* (Fig. 225, B, C.) In a survey of bilharziasis in Sierra Leone, Gordon, Davey and Peaston (1934) have shown that *B. mansoni* infection is more common in adult native women than among children or adult males. The snails (*P. pfeifferi*) proved to be susceptible to infection by *B. mansoni* but not to infection by *B. hæmatobia*; *Planorbis globosa*, however, proved susceptible to infection with *B. hæmatobia*, but not with *B. mansoni*.

The intermediary hosts of *B. mansoni* are as follows: *Planorbis boissyi* (Egypt), *P. alexandrinus* and *P. herbeni* (Sudan), *P. neosudanicus* (Nyasaland), *P. pfeifferi* (South Africa and Rhodesia), *P. philippici sub-angulatus* (Tunis), *P. gibbonsi* (Zanzibar), *P. cultratus* (Venezuela), *P. glabiatus* (North Brazil),

P. olivaceus (Brazil ; Dutch Guiana), *P. centimetralis* (Brazil), *P. guadeloupensis* (Venezuela, Antigua), *P. antiguensis* (Antilles), and *Bullinus africanus* (Natal).

Bilharzia japonica (Katurada, 1904)

Synonym.—*Schistosoma japonicum.*

The habitat of *B. japonica* in the human body is similar to that of *B. mansoni.* The adults of this species inhabit principally the veins of the large intestine, but they have been found also in the gastric, superior mesenteric, splenic, and cardiac veins ; occasionally, also, in the pulmonary arteries, rarely in others. It occurs as a natural infection in man, cat, pig, dog, horses, and cattle (*Bos sinicus*), and under experimental conditions can be transmitted to to monkeys, rabbits, mice, rats and guinea-pigs. Large numbers have been found in man at autopsy, and a count of 20,000 has been recorded from an experimentally-infected horse.

The parasite occurs commonly in Japan, China (Yangtze delta, the North River district, and Yunnan), Upper Burma (Shan States), and the Southern Philippine Islands (Samar and Leyte), in curiously restricted endemic foci, due to the local distribution of the intermediary molluscan host.

This bilharzia differs from the other two species mainly in its smaller size and the absence of tuberculations on the integument. (Fig. 226.)

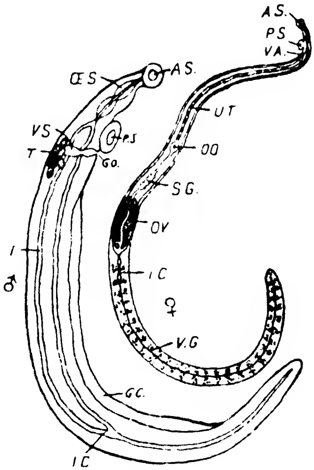


Fig. 226. —*Bilharzia japonica*, male and female. × 10.

A.S., Anterior suckers ; G.C., gynaecophoric canal ; G.O., genital opening ; I., intestine ; I.C., union of intestinal cæca ; ŒS., œsophagus ; OO., oötype ; OV., ovary ; P.S., posterior sucker ; S.G., shell-gland ; T., testes ; VA., vagina ; V.G., vitelline glands ; V.S., vesicula seminalis.

The suckers are placed close together at the anterior extremity of the body ; the acetabulum, or ventral sucker, is distinctly pedunculated or funnel-shaped ; the suckers and the ventral surface of the body in the male are provided with minute spines. Both suckers are relatively larger than those of *B. hæmatobia*. The œsophagus is provided with *two* bulbs ; the bifurcation of the alimentary canal takes place, as in *B. mansoni*, at the level of the ventral sucker, but the union of the intestinal cæca is effected more posteriorly, the united gut occupying nearly half the total body-length. The excretory system consists of two longitudinal canals which open dorsally by the excretory pore.

The **male** is 9–12 mm. in length by 0·5 mm. in breadth. The genital system consists of 6–8 elliptically-shaped testes, situated dorsally to the acetabulum. The vasa efferentia join to form a common duct opening directly posterior to it, while there is also a large seminal vesicle. The posterior portion of the body widens out, the sides overlapping one another far more extensively than in the two preceding species.[1]

The **female** is 12–26 mm. in length by 0·3 mm. in breadth. The ovary is situated in the middle of the body, and the intestinal cæca unite immedi-

[1] Great variation is to be noted in the measurements given by different authorities Katsurada has reported both male and female up to a length of 20 mm.

ately behind it. The well-developed yolk-glands extend almost to the posterior extremity. The uterus is well developed and occupies the anterior portion of the body; it may contain 50 or more eggs.

The **eggs** are oval, and are for practical purposes spineless; when seen in the fæces they measure 60–80 μ in length by 40–60 μ in breadth; on careful examination they are found to be provided with what may pass for a rudimentary lateral spine, in the form of a minute and easily-overlooked papilla like the excrescence in a cup-like depression of the shell. (Plate XXXIII, *13*, facing p. 1030.) When measured in the uterus of the female, the eggs are considerably smaller and are about 67 μ by 50 μ (Faust and Meleney).

Probably the eggs are extruded from the blood-vessels in the same

A B C

Fig. 227.—Molluscan hosts of *Bilharzia japonica.* × 10.
(*After Faust and Meleney, " Amer. Journ. of Hyg."*)

A, *Oncomelania nosophora.* B *Oncomelania formosana.* C. *Oncomelania hupensis.*

Note. These illustrations as compared with the preceding are very much enlarged to show detail.

manner as has been described in the other species; they are found chiefly in the walls of the intestine, the liver, pancreas, and mesenteric glands.

The eggs are discharged in the fæces of the vertebrate host and, when carried into water, hatch into a ciliated miracidium. The morphology of this differs little from a similar stage of *B. hæmatobia* and *B. mansoni,* but the cephalic glands, according to Cort, are smaller.

The life-history takes place in a manner similar to the preceding. After shedding its cilia, the miracidium becomes a sporocyst in the liver and hermaphrodite gland of a fresh-water mollusc, *Oncomelania nosophora,* and allied species (Fig. 227.) The sporocysts are delicate, elongated, and finger-like, and in their interior cercariæ develop. Each sporocyst is capable of giving rise to fifty or more daughter-sporocysts.

The cercariæ, which develop in the snail sixty days after infection, are similar to those already described, but are said to be smaller, being 0·48 mm. in length by 0·05 mm. in breadth. (Fig. 229.)

58

The body of the cercaria is covered with minute spines. The oral sucker is greatly developed, occupying the anterior third of the body, and is on its free margin provided with a number of minute papillæ ; there are five pairs of periacetabular glands connecting with the oral sucker by means of ducts. There is also a single pyriform gland in the head, dorsal to the digestive tube. Narabayashi states that the cercariæ are phototactic, and unable to survive a temperature above 50° C. or below 2° C. When fully formed the cercariæ escape into water and, opportunity presenting, penetrate the skin of some appropriate vertebrate, in which they attain maturity. The minute flukes can be found in the liver, measuring 150 μ. On the thirtieth day copulation takes place, and in the fifth week eggs appear in the fæces. The cercariæ reach the lungs through the pulmonary arteries, and travel *via* the mesenteric arteries, mesenteric veins, and portal vein to the liver (Meleney and Faust). It has been pointed out by Campbell that eggs of *B. japonica* may not be found in the fæces, yet be demonstrated in material removed by the duodenal sound.

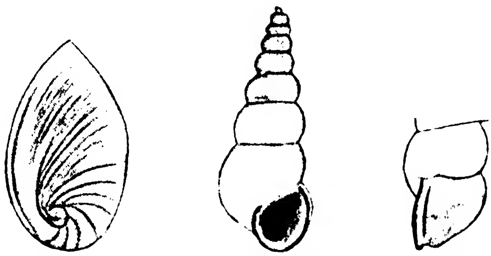


Fig. 228.—Operculum and shell of *Oncomelania nosophora.* (*After Robson.*)

A, Operculum, × 12, diagrammatic to show scheme of coiling. B, Oral aspect of shell, × 4. C, Lateral aspect of shell, showing labial swelling, × 4.

Considerable confusion has existed with regard to the correct nomenclature of the snail hosts of *B. japonica* in China and Japan.

The genus has been variously named *Katayama* (Robson, 1915) ; *Hypsobia* (Robson, 1921) ; *Blanfordia* (Pilsbury, 1915) ; and *Hemibia* (Heude, 1889).

Annandale has concluded that all the known hosts belong to a single genus, of which the correct name is *Oncomelania* (Gredler, 1881), family, *Rissoidea.*

The shells are long and narrow, with many whorls, and with the breadth increasing gradually from the apex downwards ; usually they are 5–12 mm. in height. The basal whorl is never much broader than the one above it, and the apex of the shell, when not worn away, is sharp. The mouth of the shell is ovate, broadly rounded below. The outer lip is sharp, but on the external surface there is a coarse ridge. The operculum is very thin and transparent, of ovate outline, with a small spiral figure on the inner side. (Fig. 228.)

All the species which are potential hosts of *B. japonica* in China, Japan, and Formosa live in damp places, but not in water, and bury themselves in earth when climatic conditions are unfavourable ; they continue to harbour the cercariæ during this period, but do not void them.

There is not much difficulty in recognizing this genus in China, but in

Japan it is closely simulated by the genus *Blanfordia*, whose shell is very similar in every respect, but the number of whorls is smaller and the contained snail differs considerably in having a proboscis-like snout. The following species are now recognized as carriers of *B. japonica*.

1. *Oncomelania nosophora* (Robson, 1915). The only known carrier in Japan, and probably the main one in China (Fig. 227, A).

2. *Oncomelania formosana* (Pilsbury and Hirase, 1905), distinguished from the preceding by its relatively shorter and broader shell. It appears to be the main carrier in Southern Formosa (Yokagawa) (Fig. 227, B).

3. *Oncomelania hupensis* (Gredler, 1881). This species has been discovered to be the main carrier of infection in Kiangsu, China, and closely resembles the last-named species. It is found on the banks of the hill-streams and of the canals of the plains (Fig. 227, C).

In Japan (Island of Sadi) the carrier is *Blanfordia japonica*: in the Philippines, *B. quadrasi*.

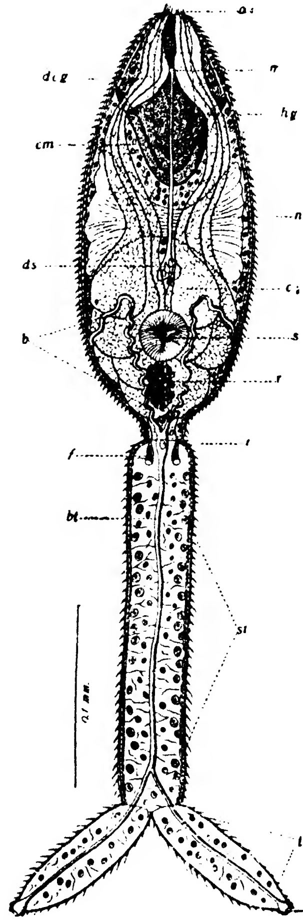


Fig. 229. — Cercaria of *Bilharzia japonica*, ventral view. × 240. (*After Cort, "Univ. of California Publications in Zoology."*)

as, Anterior spines; *b*, excretory bladder; *cg*, cephalic glands; *cm*, circular muscles; *dcg*, ducts of cephalic glands; *ds*, digestive system; *exp*, excretory pore; *f*, flame-cell; *hg*, head-gland; , island in excretory bladder; *lt*, lobe f tail; *m*, mouth; *n*, nervous system; , stem of tail; *r*, rudimentary genital cells; *s*, ventral sucker.

BILHARZIA BOVIS (Sonsino, 1876)

Bilharzia bovis, a parasite of cattle and sheep in South Africa, Southern Europe and Malaya occurs occasionally as an accidental infection in man (Cawston). The eggs may be distinguished from those of *B. hæmatobia* by being longer and narrower with a characteristic terminal spine: they are found in the fæces and urine. In Kenya the intermediary molluscan host is *Physopsis nasuta*. It is possible, however, that there has been confusion with another bovine species, *Bilharzia mattheei* (Veglia and Le Roux, 1929), which has been found by Blackie in association with *B. hæmatobia* in the vesical veins of man in Southern Rhodesia. The eggs measured 240 μ in length by 70 μ broad, and were present in the urine, and on one occasion in the fæces. The male measures 18 mm. in length by 1 mm.; the female 17–25 mm. The baboon, *Papio porcarius*, is the "reservoir host." The eggs of *B. incognita* (Chandler, 1926) have been found in the human fæces near Krishnagar, Bengal; they resemble those of *B. indica* (of cattle) but are smaller in size and less regular in outline, and are probably those of *B. suis*.

BILHARZIA CERCARIÆ

Structure of the bilharzia cercariæ.—The cercaria consists of a body and an elongated forked tail (Fig. 229), and measures about 0·48 mm. in total

length. The outer cuticle of the body and tail is beset with microscopic spines. The body contains an anterior or oral and a median or ventral sucker; the former is the larger of the two, and occupies the anterior third of the body. The central part of the sucker is occupied by oral glands; in the midline runs the œsophagus, and on either side the ducts of the conspicuous periacetabular glands, which open by small retractile papillæ surrounding the mouth. The contraction of the circular muscles compresses the ducts and expresses the secretion, indicating the method by which the cercariæ burrows into the tissues of its definitive host. The mouth opening itself is small, oval in shape, and placed on the anterior surface, while the œsophagus begins at its lower pole. The ventral sucker is smaller but more muscular than the oral; its cuticle is covered with small spines pointing to the periphery.

The periacetabular glands are five in number, and consist of large clear cells with acidophil protoplasm and conspicuous nuclei.

The primitive nerve-glanglion lies anterior to the ventral sucker; posterior to the acetabulum is a mulberry-like mass of round cells representing the primitive genital centre.

The excretory system consists of four pairs of flame-cells arranged along the margins of the body, and from these arise canals that form collecting tubules of a greater calibre which, running both forwards and backwards, meet at the posterior end of the body, and the duct is continued through the tail, where there is also one pair of flame-cells.

Cercariæ are distinctly "phototactic," and emerge from the snail in greatest numbers in direct sunlight, between 9 a.m. and 2 p.m.; on dark days there may be no emergence whatever. Their free-living existence appears to be limited to twenty-four to thirty hours. It is estimated that 50–1,000 cercariæ are discharged daily from an infected snail. The optimum temperature for this development is 32–33° C., and that of *B. mansoni* in *Planorbis pfeifferi* is from 15–35° C.

In water the cercariæ swim with ease, movement being accomplished by bending from side to side with lashing movements of the tail, which usually precedes the body, and when the surface of the water is reached the furci are stretched out at right angles so that the body and tail hang vertically downwards. When the water is disturbed the cercariæ immediately become active. Kept in a vessel or a tank, they adhere by means of the ventral sucker to the sides of the glass. In fixing on to an object the cercaria elongates itself to nearly double its normal length. Movement is effected by releasing the ventral sucker, contracting the body, and at the same time affixing by means of the oral sucker; the larva can then advance considerably. The lips of the oral sucker can be extended or retracted to a great extent; this probably serves a useful purpose and assists it in entering the skin.

After their emission from the snail the cercariæ can survive for 24–36 hours, but they require an abundant supply of oxygen.

When it comes into contact with the skin or mucous membrane of a suitable intermediary host the cercaria casts its tail, pierces the epithelium, and gains entrance into the deeper tissues. Warmth appears to be the main tactic factor. On entering the host the larva (sometimes known as a *schistosomulum*) loses its glandular cephalic cells. After an incubation period of six weeks, mature females can be found in the portal vein with well-developed eggs in their uterine cavities.

There is no general agreement as to minor details of structure in the

cercariæ of the three human species of bilharzia. There are probably some individual differences in size in various batches of cercariæ. They average about 0·4–0·5 mm. in total length. On the whole those of *B. japonica* are smaller. All have five pairs of salivary-mucin periacetabular glands.

Cercaria elvæ (Miller, 1923), a fork-tailed cercaria of a bilharzia parasite, not occurring in mammals and which emerges from several species of *Limnæa*, has been found by Cort to produce a papular eruption on the skin of human subjects exposed to this infection. A similar condition was found among bathers in a lake near Cardiff during the summer of 1928, and is known as "swimmers' itch" (*see* p. 684). In Malaya a similar condition is caused by the cercaria of *Bilharzia spindalis*, the parasite of the Indian water buffalo.

Amphistome Flukes

Gastrodiscoides hominis (Lewis and MacConnell, 1876)

G. hominis is found in the cæcum and large intestine in the Malay States, Assam, India, Cochin-China. Cases have been reported from other parts of the world, e.g. British Guiana, in immigrants from endemic areas.

The normal host of *G. hominis* in Cochin-China is the pig; it has also been found in a Napu mouse-deer from the Malay States. Fresh specimens of this parasite are reddish in colour. In the living state the body is very contractile and can be elongated to a length of 1 cm. Preserved specimens measure 5–7 mm. in length by 3–4 mm. in breadth at their widest point. The body is divided into an anterior conical and posterior discoidal portion, which forms a flattened, ventrally concave disc. On the anterior conical portion, in the midline, 2·5 mm. from the oral sucker, is a prominent genital papilla in which is situated the common genital pore. The acetabulum is situated ventrally in the caudal portion of the body. It is circular, and measures 2 mm. in diameter. The cuticle is smooth; no spines are present.

The *alimentary canal* consists of a pharynx with two pear-shaped pharyngeal pouches. The œsophagus is 1 mm. long, and ends in a muscular bulb; at this point the bifurcation of the intestine takes place, and both cæca run back as far as the anterior edge of the acetabulum.

The male genital organs consist of two lobulated testes which lie diagonally in the space between the intestinal cæca. A seminal vesicle is present, but there is no cirrus.

The ovary lies in the midline of the body posterior to the testes; it is ovoid in shape. The shell-gland lies at the side of the ovary, while the receptaculum seminis lies in front of it. The uterus is short, and lies for the most part in the space between the two testes. Laurer's canal is present.

The vitellaria lie in the middle-third of the body, and surround the posterior halves of the intestinal cæca.

The *eggs* are 152 μ in length, with a maximum diameter of 60 μ; an operculum is present.

The life-history is unknown.

Very little is known regarding the effect of this parasite on man, but it can easily be expelled from the intestinal canal by thymol treatment, and by carbon tetrachloride.

One other Amphistome, *Watsonius watsoni*, has been recorded, once only, from man. Large numbers of this fluke were found in 1904 in the upper part of the jejunum of a negro patient from South-West Africa. The normal host is probably a monkey. It has been recorded from *Cercopithecus callitrichus* in French Guinea.

CESTODES OR TAPEWORMS

It is possible to divide the cestodes occurring in man into two large orders upon the above characteristics:

i.—The Pseudophyllidea. Those with the false or slit-like suckers and elaborate internal structure.

ii.—The Cyclophyllidea. Those with cup-like or round suckers.

PSEUDOPHYLLIDEA

Diphyllobothrium latum (Linnæus, 1758; Lühe, 1910)

Synonym.—*Dibothriocephalus latus* (Linn., 1758).

This species lives in the small intestine of man, dog, cat, and bear, and is found in Europe—especially Sweden, Russia, Switzerland, and Rumania;

Asia—Turkestan and Japan; and Africa—Madagascar and Central African lakes. In recent years it has been introduced into several of the big lakes in *North America (Lake Michigan).*

Usually known as the "broad fish tapeworm," *D. latum* is greyish in colour, and may attain a length of 10 metres. Multiple infections are not infrequent. The scolex, which is 3 mm. in length, has no rostellum or hooklets, but is provided with two slit-like suckers, or longitudinal grooves, called bothria. The neck is thin, and the proglottides number 3,000–4,000.

This worm is remarkably long-lived, and has been observed in one individual for a period of thirteen years. In Leiper's experiment it lived five years. After treatment he was the only one of the three experimenters who did not expel as many tapeworms as the number of plerocercoids swallowed.

The mature segments are considerably broader than they are long. Details

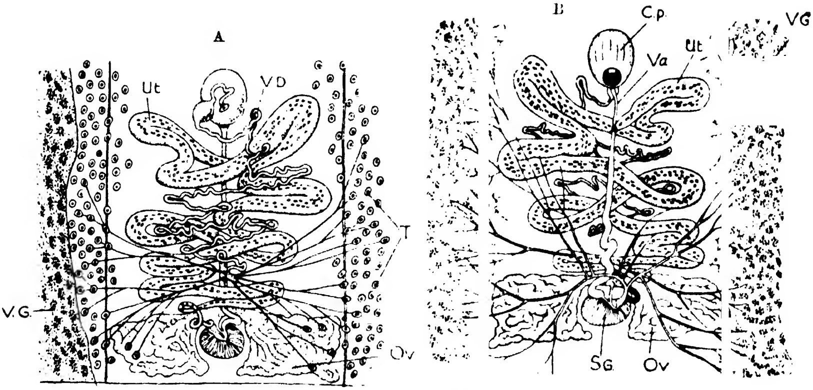


Fig. 230.—Mature segment of *Diphyllobothrium latum.* (*After Sommer and Landois, in Brumpt's "Précis de Parasitologie."*)

A, Dorsal, or male aspect. T., testes; V.D., vas deferens; V.G., vitelline glands.
B, Ventral, or female aspect. C.P., cirrus pouch; Ov., ovary; S.G., shell-gland; Ut., uterus; Va., vagina; V.G., vitelline glands.

of the anatomy of the male and female elements in each segment are shown in Fig. 230.

The eggs are brown in colour and operculated. They measure 70 μ in length by 45 μ in breadth. (Plate XXXIII, *21*, facing p. 1030.) They occur in very large quantities in the fæces, owing to the fact that every mature segment is giving birth to eggs simultaneously, and that none of the segments are being lost as is the case of the Cyclophyllidea. The life-history of *D. latum* was first worked out by Rosen and Janicki in 1918. (Fig. 231.)

After developing for three weeks in water, a ciliated embryo or onchosphere (six-hooked) appears within the egg-shell. This escapes through the operculum and by means of its cilia swims about in the water as a free-living organism for several days; at this stage it measures 22–30 μ in diameter, and it is ingested by certain fresh-water crustacea, *Cyclops strenuus, Diaptomus gracilis, D. oregonensis,* in the intestinal canal of which, within a period of two to three weeks, it is transformed into a *procercoid larva,* ovoid in form, with a terminal spherical appendix which carries the six embryonic hooks

that were present in the onchosphere. The total length at this stage is 50–60 μ. No more than two onchospheres can develop in an individual cyclops; the latter is in turn swallowed as food by fresh-water fish of many species, such as pike, perch, salmon, trout, and grayling; in Africa by certain species of barbel, and in the United States by the pike, wall-eye and burbot.

On reaching the stomach of the fish, the procercoid larva penetrates its wall and after three or four days appears in the body-cavity and becomes encysted as a *plerocercoid larva*, or *sparganum*, in the muscular and connective tissues of the flesh; it then measures 6 mm. in length. At this stage it develops characteristic cephalic grooves, nervous and excretory systems. On being ingested with raw roe (caviare), or insufficiently cooked fish, the plerocercoid develops, within a period of five or six weeks, into the adult *Diphyllobothrium* in the intestinal canal of man.

Pathogenesis. — The symptoms produced by *D. latum* are usually trifling; there is an early eosinophilia, and a severe anæmia has been known to ensue in a very small percentage of cases. This worm can be expelled by *filix mas* and *carbon tetrachloride* as in other forms of *tænia* (*see* p. 823).

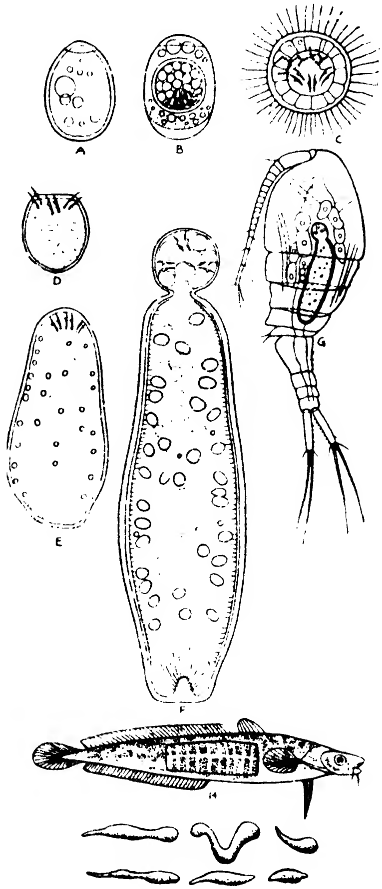


Fig. 231.—Evolutionary cycle of *Diphyllobothrium latum*. Drawn to different scales. (*Partly after Brumpt.*)

A, Egg of *D. latum*; B, hexacanth embryo; C, ciliated onchosphere or coracidium; D, E, F, development of larva, or procercoid, in *Cyclops*; G, procercoid in body-cavity of *Cyclops*; H, development of plerocercoids in fishes; J, plerocercoids of different shapes, ingested by man, dog, or cat.

Diphyllobothrium mansoni (Cobbold, 1882; Joyeux, 1928)

Synonym. — *Dibothriocephalus mansoni* (*Cobbold*, 1883).

Found in Japan, China, East Africa, Australia, and British Guiana, the adult *D. mansoni* is a common parasite of the dog, wolf, fox, cat, leopard, and tiger, and resembles *D. latum* in appearance, but differs in its more delicate structure, and in seldom attaining a length of 60–100 cm. The eggs are narrower and more ellipsoid than those of *D. latum*.

Sparganum mansoni, as it was first named by Cobbold, was first described by Manson in 1882 in making the post-mortem examination of a Chinese in Amoy; since that date about 60 cases have been reported. The subsequent experiments which determined the life-history were first carried out by Yoshida, and afterwards confirmed by Okumura.

Sparganum mansoni is the plerocercoid stage of a *Diphyllobothrium* which usually attains its adult stage in dogs and cats. Under normal conditions the plerocercoid stage is passed

in a frog, *Rana nigromaculata*, or a snake, *Elaphe climacophora*, and the procercoid stage in a cyclops, *C. leuckarti*. There are no special features in its development to distinguish it from *D. latum*.

Man becomes infected by accidentally swallowing the procercoid stage in the cyclops while drinking. He thus takes the place of the frog or snake and becomes the second intermediary host. It has also been suggested that the Chinese custom of applying split raw frogs to sores on the hands may be the chief cause of infection with *Sp. mansoni*.

The measurements of sparganum, as originally given, are 8-36 cm. in length, 0·1-12 mm. in breadth, and 0·5-1·75 mm. in thickness (Fig. 232).

The body is flat, unsegmented, and transversely wrinkled. On the ventral surface there is, as a rule, a longitudinal median groove. No sexual organs are present.

Pathogenesis.—In man the parasites may occur in practically any part of the body; they have been found in the neighbourhood of the kidneys and iliac fossæ, the pleural cavity and subcutaneous tissues. They have also been found in the urethra.

Ocular sparganosis.—Casaux and others have described this condition as frequently occurring in and about the Tonquin delta. The presence of the parasite in the orbit is

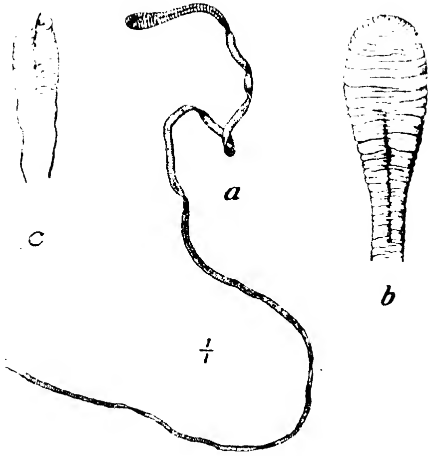


Fig. 232.—*Sparganum mansoni*, extracted from an abscess in a Masai. (*After Sambon.*)

a, Natural size; *b*, anterior extremity; *c*, posterior extremity.

characterized by pain, redness and œdema of the eyelids, with lachrymation and marked ptosis. The parasites have been found under the conjunctiva in Japan, and similar periocular swellings are reported from China. It is probable, from recent work in Indo-China, that ocular sparganosis is due to the migration of sparganum from the frog. These parasites have been recovered from the upper eyelid of a monkey experimentally infected, and human cases have been recorded one week after the application of split frogs as poultices.

Keller states that he has treated 12 cases successfully with intravenous injections of novarsenobillon. The dosage should be kept to a minimum—0·3 to 0·45 grm. for an adult—and the injection may be repeated within four or five days. Tarsorrhaphy is undertaken to preserve the cornea till the worms have been killed.

Diphyllobothrium mansonioides is regarded as the mature form of sparganum infection in America. Mueller described this as a separate species in cats and dogs. It differs from *D. mansoni* in having poorly developed bothria, with a scolex 0·2-0·5 mm. as against 0·4-0·8 mm. for *D. mansoni*.

SPARGANUM PROLIFERUM (Ijima, 1905)

This parasite, which is thought to be the larval stage of a pseudophyllid worm, has been found on two occasions encysted in the subcutaneous tissues, once in Japan and the other time in Florida.

The larvæ may be 3–12 mm. in length by 2.5 mm. in breadth (Fig. 233). The body contains calcareous corpuscles. Excretory canal and nerves are present. The parasites are usually contained in cysts, which can easily be enucleated.

In the cases reported, thousands of parasites were present in the subcutaneous tissue, intramuscular fasciæ, walls of the alimentary canal mesentery, kidney, lung, heart, and brain. The prognosis of these cases is grave, as the larvæ are liable to become disseminated throughout the body.

Nothing is known further about the life-history of this parasite.

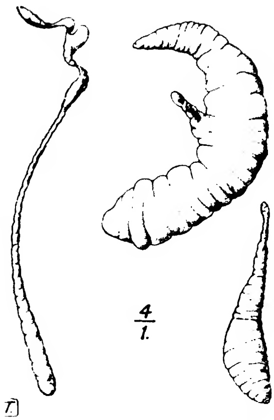


Fig. 233.—Different forms of *Sparganum proliferum*. (*After Ijima.*)

CYCLOPHYLLIDEA

Tænia solium (Linn, 1758)

Pork tapeworm

The pork tapeworm lives in the upper third of the small intestine. The specific name, *solium* probably refers to the remarkable resemblance of the rostellum to the conventional figures of the sun.

T. solium has a world-wide distribution coextensive with that of its intermediary host, the pig. For this reason it is unknown among Mohammedans, Jews, and other races that do not eat pork.

T. solium, the pork, or armed, tapeworm, generally attains a length of 2–3 metres, exceptionally 8 metres or more. The head, globular and roughly quadrangular, measures about 1 mm. in diameter. The rostrum is short, may be pigmented, and bears a double row of 25–50 hooklets. (Fig. 234, *3*.) The four suckers project slightly and are circular, each measuring 0·5 mm. in diameter. The anterior proglottides are small, but broader than long; whereas the more mature are just the reverse of this—12 mm. long by 6 mm. broad. Each proglottis bears one marginal genital pore with thick lips; the situation of the pore alternates irregularly between the right and the left margin. The uterus lies in the median plane and bears 7–10 stout diverticula. (Fig. 235, A.) The number of proglottides is less than a thousand. The terminal egg-laden and ripe proglottides become separated and pass out in the fæces, where they are capable of independent movements, even to

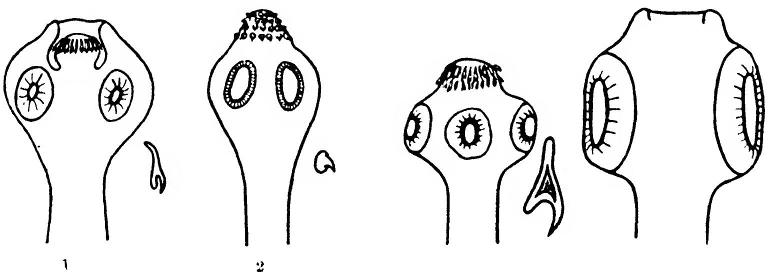


Fig. 234.—Heads of human cestodes, showing suckers and, when present, arrangement of hooklets. Diagrammatic.

1, *Hymenolepis nana* 2, *Dipylidium caninum*; 3, *Tænia solium*; 4, *Tænia saginata*.

migration outside the anus. The eggs are globular or slightly oval, 31–56 μ in diameter, and have a vitelline membrane; inside the radially striated shell is a six-hooked onchosphere (Plate XXXIII, *26*, facing p. 1030).

The mature segments become detached, four or six at a time, and pass to the exterior with the fæces, where, by process of disintegration, the eggs are set free. They are then taken into the alimentary tract of the intermediary host—in this case the pig—either in contaminated water or soiled food; man himself may exceptionally become infested in the same way. The onchosphere now passes through the gut-wall and, gaining the blood-stream, settles down in the muscular tissue, loses its hooks, and becomes a cysticercus 5–20 mm. long, generally known as *Cysticercus cellulosæ*, in which a small invaginated scolex and neck is produced resembling in miniature that of the adult tænia.

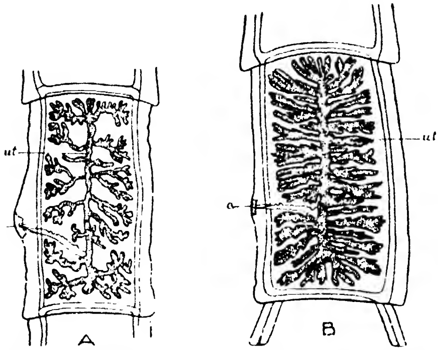


Fig. 235.—Segments of tapeworms. To show characteristic branching of uterus, as seen in mature segments.

A, *Tænia solium.* B, *Tænia saginata.* *ut.*, Uterus; *g.o.*, genital opening.

(*After R. Blanchard, in Brumpt's "Précis de Parasitologie."*)

In man, however, the cysticercus may develop in any organ, especially the muscles of the tongue, neck, or ribs; less frequently in the liver, heart, lungs, or brain, where it gives rise to epileptiform convulsions and death (*see* p. 825). *Cysticercus cellulosæ* has been recorded in the human eye; in one case it is known to have persisted there for more than twenty years. The larvæ may develop from viable eggs introduced into the gut as an accidental contamination, or as an auto-infection in a person who has become infected with the adult worm. Clinically this variety of "bladderworm" is known as *Cysticercus racemosus.*

Pork-flesh infested with this cysticercus is known as "measly pork."

When the cysticercus is taken into the alimentary tract of man, or the definitive host, the bladder is dissolved by the gastric juices, and the scolex and neck are evaginated; it then passes into the small intestine, where the scolex fixes itself to the gut-wall and proceeds to form proglottides.

The presence of the adult tæniæ in the intestinal canal of man may be unaccompanied by any symptoms in the healthy adult, but in debilitated subjects or in children it may cause gastro-intestinal disturbances, anorexia, vomiting, hyperæsthesia of nervous origin, and severe anæmia. (For treatment, *see* p. 821.)

Tænia saginata (Goeze. 1782)

Beef tapeworm

This worm lives in the upper part of the small intestine, and has a worldwide distribution—is found, in fact, wherever ox-flesh is eaten.

T. saginata, the beef tapeworm, is whitish in colour and semi-transparent; a fully adult example measures 4–10 metres, or even longer, and consists of about 2,000 segments. The scolex is pear-shaped or cubical, 1–2 mm. in diameter, with four lateral suckers, but without a rostellum or hooks; the suckers are frequently pigmented. (Fig. 234, *4*.) In place of the rostellum there is a sucker-like organ at the apex. The neck is fairly long and about half the width of the scolex. The proglottides gradually elongate as they become older; the gravid ones are three or four times longer than they are broad. The genital pore is single, and marginally-placed at the hinder end of each proglottis; in position it alternates irregularly between the right and left margins. There are 20–35 lateral branches on each side of the uterus, and these in turn may actually ramify. (Fig. 235, B.) The eggs are more or less globular, 30–40 μ long and 20–30 μ in diameter. Each is provided with two shells—the egg-shell proper, thin and transparent, and the embryophore, thick and radially striated, containing the onchosphere, with three pairs of embryonal hooklets. (Plate XXXIII, *17*, facing p. 1030.)

Several specimens of human tapeworm—*T. africana*, *T. hominis*, *T. philippina*, *T. bremneri*, *T. confusa*—have been described from time to time as belonging to new species, but they are now held to be aberrant forms or immature examples of *T. saginata*.

Abnormal forms of this tapeworm are very common, and have been described under various names—e.g. *Tænia lophosoma*.

The gravid proglottides pass to the exterior either in the fæces or independently by their own movements. Once outside the body they creep into grass or herbage, and there disintegrate. The eggs are taken into the alimentary canal of the ox, and the onchospheres are set free and pass into the small intestine. After boring their way through the intestinal wall they are carried to muscles in various parts of the body, more especially the pterygoids, the fatty tissues surrounding the heart, the diaphragm, and the tongue. Here they become cysticerci, as in the analogous *T. solium*, 7·5–9 mm. in length by 5·5 mm. in breadth. The cysticerci can live for eight months or thereabouts in the ox, and can only develop further when ingested by man, the definitive host. When this happens the bladder is digested and the liberated scolex passes into the small intestine and affixes itself by means of its suckers to the gut-wall. It is found that the cysts die when heated to a temperature of 48° C.

In the definitive host the parasite may give rise to slight symptoms or may cause a certain degree of anæmia. (For treatment, *see* p. 821.)

Larval Forms of Tænia occurring in Man

Hydatid, the larval form of *Echinococcus granulosus*, the adult of which occurs in the intestine of the dog.

Cysticercus cellulosæ, the larval form of *T. solium*, in normal circumstances occurring in the pig, but also in man.

Cysticercus bovis, the larval form of *T. saginata*, which normally occurs in the muscles of the ox, but has been reported in man on a very few occasions.

Cœnurus cerebralis, the larval form of *Tænia* (*Multiceps*) *multiceps*, normally

occurs in the brain of sheep, and passes the adult stage in the intestine of the dog. One case has been recorded in man.

Cœnurus glomeratus has once been found in a cyst on the chest-wall in man in Northern Nigeria, and is normally found in the gerbille. The hooks of the scoleces are distinctive.

Echinococcus granulosus (Batsch, 1786)

Hydatid; Tænia Echinococcus

The adult worm is a parasite of the dog, wolf, jackal and fox, and occurs in the small intestine of these animals. It is common in Iceland; in Asia—especially in Arabia; in Africa—Algeria, Tunis, Egypt, Abyssinia, and the Cape; in America—Argentina and Uruguay; in Australia—Victoria and Tasmania.

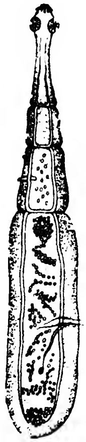


Fig. 236. *Echinococcus granulosus.* × 15. (*After Leuckart, in Brumpt's "Précis de Parasitologie."*)

The larval stage of this parasite is the most striking, for after ingestion of the egg by the intermediate mammalian host (sheep, cattle, pigs, camels or man), a hydatid cyst forms in the organs of the body, especially the liver.

E. granulosus (Fig. 236) is one of the smallest of tapeworms, 2·5–6 mm. in length. The scolex is 0·3 mm. in diameter, irregularly globular in shape, and is provided at its apex with a projecting rostellum which carries two circular rows of hooks of varying size and number. The neck is short and thick. The proglottides do not number more than four, of which the terminal one is by far the longest, measuring 2–3 mm. in length; it is the only one which is sexually mature, and may contain as many as 800 eggs. The genital apertures are marginal, one to each proglottis, and have an alternate arrangement. The testes are spherical and numerous; the cirrus pouch is large and pear-shaped. The uterus, tubular, and median in position, has short unbranched lateral diverticula. The eggs are slightly ovoidal in shape, 32–36 μ in length and 21–30 μ in breadth. The onchosphere is provided with three pairs of embryonal hooklets.

The egg is swallowed and in the stomach the shell is digested as the onchosphere escapes. Eight hours after ingestion the parasite appears in the portal vein and reaches the liver, whence the embryos become filtered out; the next filter is the lungs, where a smaller number of embryos become lodged. In three weeks it has become vesicular and just visible to the naked eye. In three months it has become 5 cm. in diameter, and within five has doubled its size. The wall of the hydatid cyst is composed of an outer laminated fibrous layer formed by the host, a thick median striated layer secreted by the cyst, and an inner "germinal layer" from which brood-capsules and daughter-cysts arise (Dévé and Dew).

Two types of development occur, (1) endogenous, (2) exogenous. In the former, proliferation takes place inwards towards the cyst-cavity, while in the latter it takes place in an outward direction. The varieties of hydatid are so striking that subspecies of Tænia have been described, especially in *alveolar* hydatid, which has a limited geographical distribution.

Brood-capsules are formed from small nuclear masses of the parenchy-

matous germinal layer; later these become vacuolated to form vesicles. The larval scoleces arise from a local thickening of the wall of the brood-capsule. The wall of the capsule evaginates to form a protective cup for the growing scolex, but near the head end the cuticle thickens and a circle of hooklets develops. There is a contractile part of the body of the scolex capable of invaginating the head, so that the typical resting position of the scolex has the hooklets inside. (Fig. 237.) The free brood-capsules and the free scoleces in the cavity of the hydatid cyst are commonly known as "hydatid sand."

Daughter-cysts arise inside the cyst, being produced by some injury or mechanical interference with the mother-cyst. They most commonly arise from the detached germinal layer, but may also develop from brood-capsule cells, or, rarely, by vesicular changes from detached scoleces. Daughter-cysts in the liver are usually bile-stained. Dévé and Dew found that intramuscular

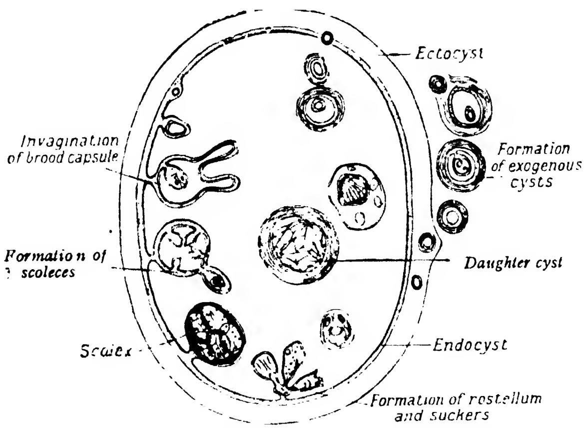


Fig. 237.—Schema of hydatid cyst. (*After Blanchard.*)

or subcutaneous injection of scoleces gives rise to new cysts. This would account for the dissemination of hydatid cysts through the body as sometimes happens after operation.

Exogenous daughter-cysts, which in man are found in the omentum and in bones, are secondary and are caused by herniation or rupture of both germinal and laminated layers through the weakened parts of the adventitia resulting from intracystic pressure. By the final exclusion of these herniations new cysts are formed.

Multilocular cysts are sometimes found, especially in the lungs. In the liver a multilocular, or *alveolar*, hydatid was originally described by Virchow. It forms a solid tumour which on section looks like a sponge. The development of this lesion is characterized by a double process—a peripheral infiltration of the liver by the parasitic elements and central necrosis of the parasitized mass. The metastatic lesions of this variety are remarkably constant, no matter what organ may be attacked.

Dogs, foxes and jackals become infected with the adult parasite by eating the various organs, especially the discarded offal, of sheep, in which hydatids

occur. The cyst-wall becomes digested and the young tapeworms escape into the small intestine in the customary manner.

Man becomes infected by too close association with the common definitive host, the sheep-dog. The eggs are ingested by using the same dishes as these animals, or by kissing infected dogs; and it is also possible that houseflies may disseminate the eggs from the fæces of these animals. Persons of all ages are liable to infection, but the disease known as hydatid is more common in children under ten years. The symptoms to which hydatid may give rise are very varied, according to the site of the cyst. They may include symptoms of toxæmia, such as pyrexia, urticaria, and multiform cutaneous eruptions. On the other hand, the fully-developed cyst may appear as a tumour, especially in the liver, and this, on bursting, forms secondary cysts in other organs, or may suppurate and cause general peritonitis. In the brain, hydatids give rise to symptoms of cerebral tumour; while those of the liver, spleen, and peritoneum are liable to simulate malignant growths. Hydatids of the lung give rise to symptoms of compression, with the formation of fluid in the pleural cavity. The kidney may be converted into a mass resembling hydronephrosis.

Diagnosis.—The cystic swelling may possess peculiar physical signs. If it is situated near the surface, a fluctuation, known as the "hydatid thrill," may be elicited, but if it is deeply seated this is of little value. On puncture of the cyst with an exploratory syringe the scoleces and hooklets may be recognized under the microscope.

Three aids to diagnosis have been described: (1) The precipitin reaction (Welch and Chapman), in which equal parts of preserved hydatid fluid and serum of the suspected case are mingled, the mixture then being incubated for one hour at 37° C. Should the case be infected, a precipitate forms; but one should note that exceptionally this reaction may be given by normal serum. (2) The complement-deviation reaction of Weinberg and Parvu, for which the generally-accepted Wassermann technique is employed, using hydatid fluid (0·4 c.c.) as the antigen. Fairley considers that the best antigen is obtained by macerating the scoleces with absolute alcohol; neither the extract of the cyst-wall nor dried hydatid fluid is satisfactory. Difficulty has so far been experienced in preserving the antigen in an active state. (3) The Casoni, or intradermal test, has been well reported upon by Kellaway and Dew, who find it of diagnostic value in 90 per cent. of hydatid cases. The fluid is obtained from sheep hydatid, and a few drops are instilled by means of a hypodermic needle into the layers of the skin. Within ten minutes of injection, in a positive case, there is produced a large wheal, surrounded by a wide zone of erythema. This fades in an hour, to be followed in six to eight hours by a very large erythema with infiltration and œdema of the subcutaneous tissues. This reaction may be present for several years after surgical removal of the cyst.

Life-history and pathogenesis.—There are two forms of hydatid which occur in man—unilocular and multilocular (or alveolar) hydatid; the former is by far the more common and important. Development takes place as follows: The gravid proglottis is evacuated with the fæces of the host, and by disintegration the eggs are set free. The larval form can develop in other mammals besides man—chiefly in the sheep, ox, pig, camel, goat, and rabbit—and may give rise to severe or, it may be, fatal symptoms. The onchosphere, having passed through the intestinal wall, develops into an hydatid cyst in the liver, lungs, kidney, peritoneum, brain, or genitalia,

but occasionally also in other situations, such as the long bones, the heart, and the orbital cavity. The bladder thus produced may attain the size of a human head; surrounding it there develops a fibrous layer formed from the host's tissues. The cyst-wall itself consists of two layers: (*a*) a cuticular, or laminated layer, composed of a chitinous substance; (*b*) a germinal layer, made up of an outer layer of small cells and an inner layer of larger ones, together with some muscular fibres, calcareous bodies, and glycogen. The bladder itself is filled with a clear. watery fluid with a specific gravity of 1007–1015, often containing a trace of albumin which is not coagulable by heat or acids, and which is possibly a protein allied to casein. Sodium chloride is present to the extent of 0·5 per cent.; phosphates and sulphates of soda. succinates of sodium and calcium, traces of sugar and inosite are also present. The intracystic toxin is most nearly allied to albumin. The alarming symptoms produced by the accidental rupture of a cyst are probably anaphylactic in nature.

There are two forms of *unilocular* hydatid—primary and secondary; the one is caused by the ingestion of the hexacanth embryo passed in the dog's fæces, as described above; the other by the implantation of a scolex which has been set at liberty by the rupture of a primary hydatid cyst. This scolex undergoes vesicular transformation, and continues to develop on the same lines as a primary hydatid.

Under the designation *multilocular*. or *alveolar hydatid*, several authorities have described the larval stages of an echinococcus which differs from the development as given above. It was thought that the adult tapeworm might be a different species, and not *E. granulosus*, but this has been proved by Dew to be incorrect. The initial larval stages follow the same development as *E. granulosus*, but after a certain stage of development has been attained, the original cyst throws off germinal buds, which become multilocular or alveolar cysts. The liver is generally the seat of this infection, and appears honeycombed with the cysts, which have no cyst-wall.

Fig. 238.
Hymenolepis nana.
Magnified.

Surgical treatment in this case is almost impossible, though partial hepatectomy has been practised with apparent success by Brins.

The multilocular form has a peculiar distribution, being found in the Tyrol, Würtemberg, Russia, and Siberia.

Hymenolepis nana (Siebold, 1852)

Synonyms.—*Tænia nana*; *Hymenolepis murina*; *H. longior.*

H. nana was originally discovered by Bilharz in Cairo in 1851; Grassi later believed it to be identical with *H. fraterna* of the rat, a view which has been confirmed by Woodland as the result of his work in Lisbon.

H. nana is limited to warm countries. It is found in Egypt, the Sudan, Siam, Japan, the Southern States of the American Union, Brazil, Argentina, and throughout Europe but more especially in the warmer parts, as in Portugal, Spain, and Sicily, where, according to Calandruccio, 10 per cent. of the children are affected. This species inhabits the small intestine.

The strobila of *H. nana* varies in length from 5–45 mm. with the number of proglottides, which may be 100–200. (Fig. 238.) The scolex is subglobular and measures 139–480 μ

in diameter; it is provided with a well-developed rostellum armed with a single crown of 20–30 hooklets 14–18 μ long; the suckers are globular, and have a diameter of 80–150 μ. (Fig. 234, *1*.) The neck is long. The proglottides are very short anteriorly; farther down they increase in size, but remain broader than long. Only the hindmost segments may equal or even slightly exceed their breadth. The maximum breadth of the proglottides is 0·5–0·9 mm. The genital pores open on the margin near the anterior border of each segment. There are three testes in each segment; the vas deferens widens to form a seminal vesicle. The gravid uterus occupies nearly the entire segment. The eggs number 80–180 in each proglottis: they are oval or globular, and present two distinct membranes; the outer one measures from 40–46 μ in diameter, the inner one 20–34 μ. (Plate XXXIII, 20, facing p. 1030.) The latter exhibits at each pole a more or less conspicuous mammillate projection, and encloses an onchosphere with three pairs of embryonic hooks. The segments, when set at liberty, are partially digested; the eggs are set free and appear in the fæces, where they can be found by microscopical examination.

No intermediary host is required, but the larval parasite can enter a villus of the small intestine and become a cysticercoid or a *cercocystis*,[1] the probable mode of evolution being based upon the analogous case of *H. fraterna* in the rat, as worked out by Grassi and Rovelli, and later confirmed by Joyeux, Woodland, and Scott.

In about 40–70 hours after ingestion the scolex has appeared, and in 80–90 hours the rostellum is provided with hooklets. Then the parasite passes into the lumen of the intestine, where it can be seen attached to the epithelium of the villus with short neck and no trace of segmentation. The rapidity of development varies somewhat, and, as a rule, various stages are found occurring simultaneously in the same host. Strobilization is rapid; the proglottidet attain maturity in about 10–12 days, and about 30 days after infection the eggs of the parasies begin to appear in the fæces. The development of the parasite without the aid of an intermediary host and without passing out of the body of the definitive host forms the single exception to the rule that cestodes do not multiply in the body of the definitive host.

H. nana is very minute, but, as a rule, it occurs in large numbers—usually hundreds, not infrequently thousands. The most frequent symptoms reported by authors are abdominal pain, which may, or may not, be associated with diarrhœa; convulsions of various kinds, frequently epileptiform; headache and strabismus. The nervous phenomena are ascribed to the absorption of toxic products elaborated by the parasite. On account of its small size it is easily overlooked. Diagnosis is based on the presence of the characteristic eggs in the fæces. Some care is requisite in looking for the eggs, because, owing to their transparency, they may escape observation.

Treatment.—*H. nana* is expelled by male fern or by oil of chenopodium and carbon tetrachloride, but, in the Editor's experience, is not easy to dislodge. A patient harbouring this parasite should not sleep in the same bed with another person.

HYMENOLEPIS DIMINUTA (Rudolphi, 1819)

H. diminuta is a parasite of rats (*Rattus decumanus*, *R. rattus*, and *R. alexandrinus*) and mice (*Mus musculus* and *M. sylvaticus*), and has been found in man in Italy, South America, the Congo, where it is quite common (Chesterman), and the West Indies, some seventeen cases having been reported.

The length is 20–60 cm., the breadth 3·5 mm. The head is very small, cuboidal in shape, with a small infundibulum at the apex in which is a rudimentary rostellum; there are four small suckers, unarmed. The neck is shorter than the head, and the proglottides increase in size, but are considerably broader than long. The eggs as they appear in the fæces are circular or slightly ovoid, measuring 60–86 μ in diameter; the outer shell is yellowish and thickened, with indistinct radiations containing a hexacanth onchosphere.

The cysticercus stage takes place in the body cavity of certain insects, especially of fleas, *Nosopsyllus fasciatus*, *Xenopsylla cheopis*, *Pulex irritans*, and also certain coleoptera and lepidoptera, *Asopia* (*Pyralis*) *farinalis*, *Anisolabis annulipes*, *Akis spinosa*, and *Scaurus striatus*. Bacigalupo lists *Dermestes vulpinus*, *D. peruvianus*, *Ulosonia parvicornis* and *Embia argentina* as intermediary hosts in South America.

The rat itself is said to be easily parasitized by eating infected fleas. The cysticercoids, when ingested by their definitive host, become adult in 17 days.

DIPYLIDIUM CANINUM (Linn., 1758)

D. caninum is a common parasite of dogs, cats, and jackals. There are almost 100 records of its occurrence in man, most of them in children in European countries, and it lives in the small intestine.

[1] The term cercocystis was introduced by Villot to designate those cysticercoids which are provided with caudal appendages.

The strobila measures 15–40 cm. in length and has a maximum breadth of 2–3 mm. The scolex is a small and globular point 0·55 mm. in diameter. The rostellum, which can be retracted into an infundibulum, has three or four circles each consisting of 28–30 small hooklets, 14–18 μ in length. These hooklets are of a characteristic "rose-thorn" shape. There are four elliptical suckers. (Fig. 234, 2.) The proglottides are very narrow, and number 200 or more; the more mature measure 2–3 mm. in breadth and 6–7 mm. in length, so that they are considerably longer than broad.

There are two sets of genital apparatus in each segment, and the genital pores lie symmetrically at the lateral margins. The uterine cavities contain egg-nests, each with 8–15 eggs, which are round and measure 35–40 μ in diameter. The mature proglottides leave the intestine spontaneously.

As a rule, *D. caninum* infections produce no untoward symptoms. The larval or cysticercoid stage takes place in the dog-louse (*Trichodectes canis*), in the dog-flea (*Ctenocephalus canis*), or in the human flea (*Pulex irritans*).

According to Joyeux, the eggs are eaten by the larval flea, but the development of the hexacanth embryo, which lies in the adipose tissue and muscles of the flea, is delayed until the stage of the adult flea is reached. Infection in man is caused by swallowing an infected adult flea. Treatment by *Filix mas* is the same as for other tapeworms.

Davainea

The genus *Davainea* is characterized by the presence of numerous hooklets on the suckers, as well as on the rostellum, where they are of a characteristic "coal-hammer" shape. The genital pores are usually unilateral; in the ripe segments the uterus contains eggs. Normally, members of this genus are parasites of birds; more rarely, of mammals.

Three species have been recorded from man: (1) *Davainea asiatica*—one case from Russian Turkestan; (2) *D. formosana*—one from Formosa; and (3) *D. madagascariensis*—eight cases from Mauritius, Siam, the Philippines, and British Guiana.

The life-history is unknown.

NEMATODES, OR ROUNDWORMS

The nematodes are cylindrical non-segmented worms, usually tapering at both ends; in colour they are white or yellow, sometimes semi-transparent.

For illustrations of eggs of nematodes found in man, *see* Plate XXXIII.

Ascaris lumbricoides (Linn., 1758)

Round Worm

This worm inhabits the small intestine of man and the gorilla. *A. suilla* of the pig is indistinguishable, morphologically, from *A. lumbricoides* occurring in man, and has a world-wide distribution.

The female measures 20–35 cm. by 3–6 mm. in breadth, the male 15–31 cm. by 2–4 mm. In colour they are pale yellow or brown, with whitish longitudinal lines; in shape they are round, and taper at both ends. The mouth opens at the anterior end, and is guarded by thin lips which have finely denticulated margins. (Fig. 239.) The anus is subterminal. In the female there are paired genital tubes, each member containing uterus, receptaculum seminis, oviduct, and ovary. It is estimated that the tubules and ducts may attain a length of 1,250 mm. The total capacity of the genital tubules at any one time is estimated at 27 million eggs and the average daily output at 200,000. In the male the tail is curved into a semicircle; there are two rows of tactile papillæ and two short chitinous spicules.

The eggs (Plate XXXIII, *7, 8, 9, 10,* facing p. 1052) are elliptical, 50–70 μ in length by 40–50 μ in breadth, and are encased in a rough albuminous coat, giving them a mammillated appearance. They are usually more or less intensely stained by the fæcal pigments.

In the fæces the eggs exhibit no trace of segmentation or of differentiated embryo; but if placed in water, or kept moist and in a warm place, in the

course of one or more months—longer or shorter according to temperature—the larva is developed, and can be seen coiled up and moving about inside the egg-shell. Formerly it was held that, if such an egg were accidentally or intentionally swallowed, on arrival in the stomach, the shell would be dissolved away and the contained rhabditiform larva set free; in a month it would grow into a sexually mature animal, and, if both sexes were present, eggs in countless numbers would soon be produced in the fæces.

This view of the life-history of *A. lumbricoides* was based on numerous experiments on man by Continental observers, and seemed to be justified. Stewart, however, has shown that, if ripe ascaris eggs are fed to mice and certain other rodents, the larvæ, or a proportion of them, on being hatched out, bore their way into the liver and lungs. In the latter organs they appear in about a week's time, and, if the dose of eggs has been a large one, may cause fatal pneumonia. In experiments made on sucking-pigs, this investigator found that exactly the same process takes place as in rats

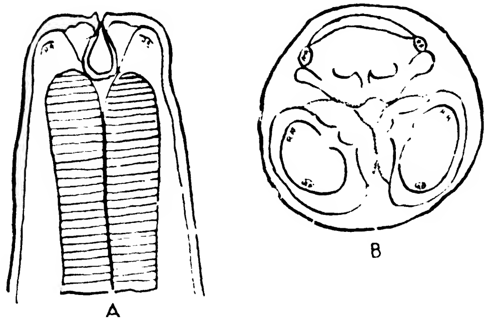


Fig. 239.—Head of *Ascaris lumbricoides*; (A) ventral view; (B) anterior view, showing oral labia. (*After Faust.*)

and mice. For instance, he has found the larvæ abundant in the lungs and trachea on the eighth day; on the ninth they begin to travel down the alimentary canal, and on the following day appear in considerable numbers in the fæces, especially in the colon and cæcum. They measure 1·3–2 mm. on the tenth day, and 1·75–2·37 mm. on the fifteenth. (Fig. 240.)

Sometimes the larvæ migrate into aberrant foci such as the peripheral glands, the thyroid, thymus, and spleen, and even into the brain and spinal cord, giving rise to odd symptoms.

Later observations by Yoshida, Ransom, Foster, Fülleborn, and Brumpt have confirmed this work on guinea-pigs, rabbits, goats, sheep, and monkeys, while the experiments of Mosler and Lutz indicate that the same process takes place in man. It was proved by Yoshida by experiment on himself that the larvæ from the lung of the rat 8–10 days old became adults in the intestine after a short space of time. Porcine ascaris larvæ in man and ascaris larvæ in the pig are apparently unable to complete their development. Immature ascaris worms 1–10 cm. in length are frequently spontaneously evacuated from the bowel. An account of the pathogenic effects of the parasite is given at p. 803.

Respiratory symptoms commence twenty-six hours to four or five days after ingestion of eggs and a clinical picture of lobar pneumonia is produced

by the migration of the larvæ to the lung. This has occurred in controlled human cases such as that of the brothers Koino in 1922, and the disease is sufficiently striking to warrant the designation of *Ascaris* pneumonia.

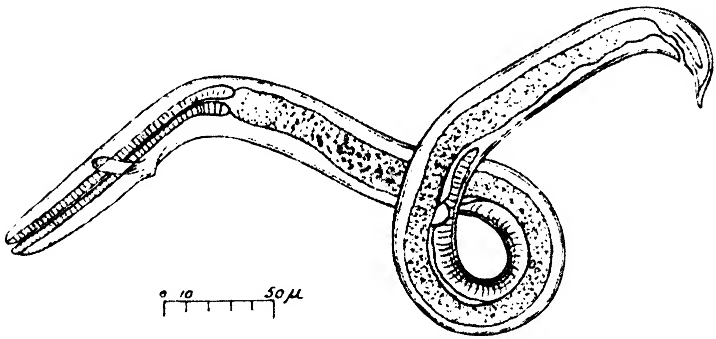


Fig. 240.—Larva of *Ascaris lumbricoides* recovered from the trachea of a rat eight days after ingestion of the eggs of the parasite. (*After Brumpt's "Précis de Parasitologie."*)

It may also give rise to severe symptoms in its wanderings in the intestine and may cause intestinal obstruction.

PHYSALOPTERA CAUCASICA (v. Linstow, 1902)

Synonym.—*P. mordens* (Leiper, 1907).

This worm lives in the œsophagus, stomach, and small intestine, occasionally the liver. The normal host is a monkey. It is quite common in natives in Central Africa, and is found in Portuguese East Africa, Uganda, and Nyasaland.

Both sexes are provided with a mouth guarded by two large lips, each of which is armed with two papillæ and two small rows of teeth. (Fig. 241.)

The *male* is 14–50 mm. in length and 0·7 to 1 mm. in breadth; the tail end is provided with two lateral alæ which are formed by expansion of the cuticle, supported by four pairs of pedunculated papillæ. In addition to these there are six pairs of sessile papillæ and one unpaired postanal papilla. There are also two spicules of unequal length.

The *female* measures 24–100 mm in length and 1·14–2·8 mm. in breadth; the posterior end tapers rapidly, terminating in a sharp point. There are two ovaries and a single uterine tube, and the vulva is situated in the anterior part of the body. The eggs measure 45 μ in length and 35 μ in breadth, and are provided with a thick, smooth shell. The life-cycle is quite unknown, but it is believed that insects serve as an intermediary host. The clinical aspects of this infection have not been studied.

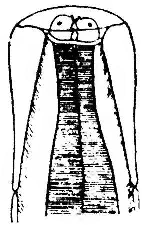


Fig. 241.—Head of *Physaloptera caucasica.* (*After Leiper.*)

ANCYLOSTOMA DUODENALE (Dubini, 1843)

"OLD-WORLD HOOKWORM"

This parasite lives in the small intestine of man, occasionally in the tiger, young dogs, and cats. Originally confined to Europe, it has now spread to America, Africa, and Asia, and is found even in northern countries, Germany and England, wherever humidity and temperature are favourable to its development, e.g. the Simplon tunnel and the tin mines of Cornwall.

It is very common in Egypt, where it is the sole representative of the hook-worm in man.

Both sexes are cylindrical; *in colour they are white, grey, or reddish-brown from the presence of blood.*

The *male* measures 8–11 mm. in length and 0·4–0·5 mm. in breadth. (Fig. 242.) A copulatory bursa is present, the dorsal ray of which

An., anus; *co. ceph.*, cephalic nerve commissure; *gl. cerv.*, cervical gland; *nu. gl. cerv.*, nucleus of cervical gland; *d. ej.*, ejaculatory duct; *te.*, testes; *v.s.*, vesicula seminalis; *spic.*, spicules; *vulv.*, vaginal opening; *pap. cerv.*, cervical papilla; *p. ex.*, excretory pore.

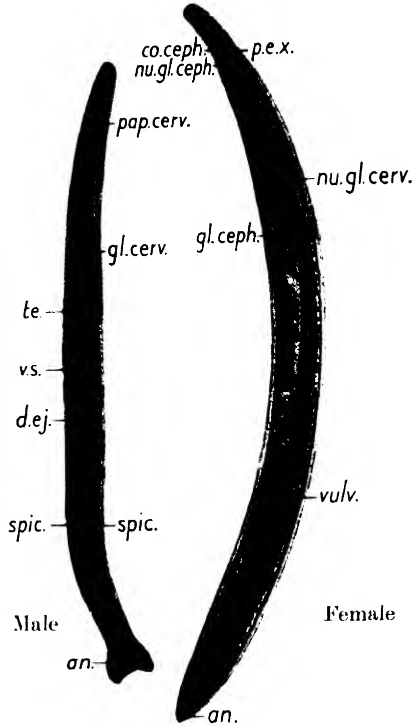


Fig. 242.—*Ancylostoma duodenale*, **male and female.** × 14. (*After Looss.*)
(For actual size, *see* Fig. 166.)

is divided towards the distal end into smaller rays, which in turn bifurcate into three unequal portions (Fig. 244). Two long and very delicate spicules are present.

The *female* measures 10–13 mm. in length by 0·6 mm. in breadth. (Fig. 242.)

The number of ancylostomes recovered at autopsy may number 500–1,000 or more. Individuals are apparently long-lived, their life-span being between four and five years. The interval between active infection and the disappearance of eggs from the fæces averages, according to Kendrick, about seventy-six months. The maximum egg-output is reached in a period of fifteen to eighteen months after infection. The body is cylindrical and slightly expanded posteriorly. The vagina is situated in the posterior third of the

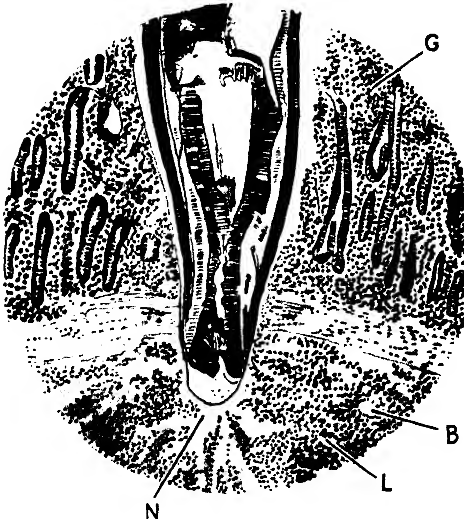


Fig. 243.—Section through the duodenum showing the method of attachment of the ancylostome to the wall. (*After Esmeja.*)

L., leucocyte infiltration; N., zone of necrosis; B., blood-vessels; G., glands of Lieberkuhn disrupted by the ancylostome.

body. The greater part of the body-cavity is occupied by the ovary and much-coiled uterine tubes, containing characteristic eggs. Owing to the situation of the genital openings in both sexes, the worms in copulation assume a Y-shaped figure.

There are two well-marked cephalic glands, which occupy the anterior third of the body in both sexes, and secrete a ferment that prevents the clotting of blood (Fig. 243). The buccal capsule is lined with chitin, and contains

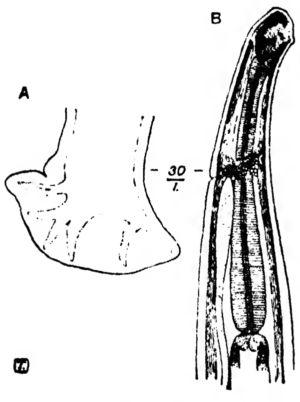


Fig. 244.—Bursa (A) and head (B) of *A. duodenale* ♂ (*After Looss.*)

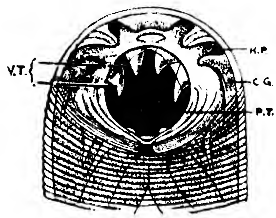


Fig. 245.—Head of *A. duodenale*, **showing hook-like ventral teeth.** × 50. (*After Looss.*)

C.G., Cephalic gland; H.P., head papillæ; P.T., pharyngeal teeth; V.T. ventral teeth.

two pairs of sharp teeth, which lie on the ventral aspect of the buccal cavity; the opening of the mouth is not terminal, but is directed towards the dorsal surface (Fig. 245). The *eggs*, elliptical in shape, with a transparent shell, measure 60 μ in length by 40 μ in breadth. When freshly deposited they contain 2-4 blastomeres each. (Fig. 246, Plate XXXIII, *14*, facing p. 1025.)

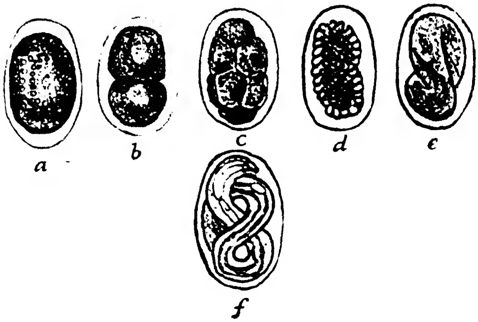


Fig. 246.—Developmental stages of the larva in eggs of ***A. duodenale.*** **(*a*). (*b*) and (*c*) are seen in fresh stools; (*d*), (*e*) and (*f*) when the stool is stale.** × 300. (*After Looss.*)

For more details of life-history and pathogenesis, *see* pp. 806–813.

Ancylostoma braziliense (Gomez, 1910)

This parasite was originally found in dogs and cats in Brazil; shortly afterwards it was described, under the name of *A. ceylanicum*, in the civet cat in Ceylon. For a long time these were considered to belong to two distinct species, but they are now regarded as identical.

A. braziliense is found to be fairly common in mixed "hookworm" infections in man in India, the Malay States, and Siam. It is considerably smaller than *A. duodenale*, and the internal pair of ventral teeth are very much smaller than the corresponding teeth of *A. duodenale*. The formation of the rays in the copulatory bursa also differs (Fig 247) The male is 8·5 mm. in length, and the female 10 mm.; the former has a distinctive bursa. The eggs of *A. braziliense* are indistinguishable from those of *A. duodenale*. The larvæ frequently penetrate the human skin and in doing so cause an extensive and irritating eruption. Kirby-Smith, Dove and White (1925-1928) have shown that it is this species which is responsible for the "creeping eruption" of the Southern United States (*see* p. 852). The signs and symptoms of this infection, according to Bonne, do not differ from those produced by *A. duodenale*.

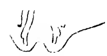


Fig. 247.—Dorsal ray of ***Ancylostoma braziliense.*** (*After Leiper.*)

Necator americanus (Stiles, 1902)

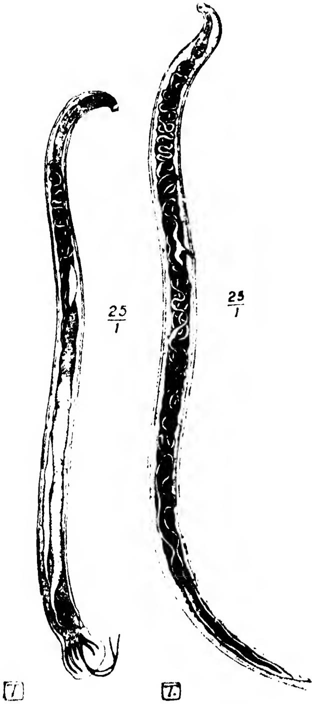
N. americanus lives in the small intestine of man; it also occurs in the gorilla, Patas monkey, and rhinoceros.

This species was originally discovered by Stiles in cases of ancylostomiasis in America, though its range is by no means confined to the New World, as its name would seem to indicate. It has been found southwards from Virginia to Brzil, in Central and West Africa, in India, Ceylon, the Pacific islands, Malaya, and the Philippines. Probably it is as widely diffused as *A. duodenale*, in Ceylon and India it is the commonest species encountered.

Originally a parasite of Africa and Asia, it was introduced into the New World by African slaves.

N. americanus (Fig. 248) is a shorter and more slender worm than *A. duodenale.*

The *male* measures 7–9 mm. in length by 0·3 mm. in breadth. The caudal bursa possesses a short dorso-median lobe which appears as if divided into two ; the dorsal ray branches at its base into divergent arms with bipartite tips, instead of tridigitate as in *A. duodenale.* The common base of the



Male. Female.

Fig. 248. *Necator americanus.* × 12. (*After Placencia.*)

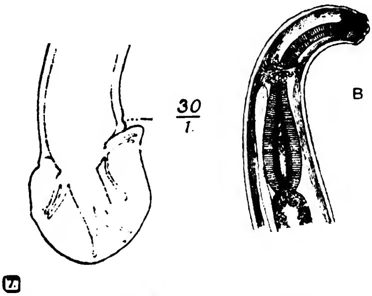


Fig. 249.—Bursa (A) and head (B) of *N. americanus.* (*After Looss.*)

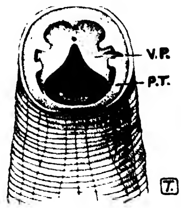


Fig. 250.—Head of *Necator americanus,* showing pharyngeal teeth (P.T.) and ventral plates (V.P.). × 50.

dorsal and dorso-lateral rays is very short. (Fig. 249.) There are two separate spicules, which unite to form a single terminal barb.

The *female* measures 9–11 mm. in length by 0·4 mm. in breadth. The vulva is placed slightly in front of the middle of the body. Copulation of sexes, as in the *A. duodenale,* takes place at the same Y-shaped angle. The pathogenic effects are similar to those of the preceding species (p. 809).

The buccal capsule is smaller than in *A. duodenale* and presents an irregular border ; in place of four hook-like teeth, it has a ventral pair of cutting plates ; the pair of dorsal teeth is likewise represented by a

pair of slightly developed chitinous plates of the same nature. The outlet of the dorsal gland, usually called the dorsal rib or tooth, projects prominently into the oral cavity. Deeply placed in the capsule are one pair of dorsal and one pair of ventral submedian lancets. (Fig. 250.) The eggs are slightly larger than those of *A. duodenale*, and measure 64–75 μ in length by 36–40 μ in breadth.

Summary of the life-history of the hookworms.

Eggs (Fig. 246).—Deposited in the human intestine, with two, four, or eight blastomeres; on reaching the outer world they give rise in twenty-four hours to—

Rhabditiform larvæ.—Moult on the third day; on the fifth day the pharyngeal bulb disappears; a second moult takes place and they become filariform larvæ, having a simple muscular œsophagus and a protective sheath; this is the infective stage, and they gain entrance to the body by penetration of the skin or buccal mucous membranes. (Fig. 251.)

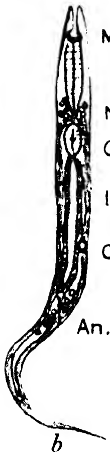


Fig. 251.—(*a*) Mature larva; (*b*) rhabditiform larva × 120; and (*c*) head of larva of *A. duodenale*.
M., mouth; N., nerve-ring; Oes., œsophagus; Int., intestine; Gen., genital cell; An., anus.
(*Partly after Looss.*)

On penetrating the skin the sheath is left behind, and the larvæ enter the lymphatics, whence they gain the blood-stream and make their way to the lungs, which they reach on or about the third day. Breaking through the thin-walled alveoli and the lung, they effect entrance into the bronchi, thence *via* the trachea and œsophagus into the stomach; during this migration the third moult takes place, and a terminal buccal capsule is formed. On arrival in the intestine, which occurs about the seventh day, the fourth moult takes place, and the terminal buccal capsule is changed for what is known as a "provisional buccal capsule," which has a mouth-opening directed dorsally as in the adult worm, but has no teeth. On or about the fifteenth day after entry into the body the provisional buccal capsule is cast, and the worm takes on its adult form, both the adult buccal capsule and bursa of the male being now developed. The worms become sexually mature in three to four weeks, copulation takes place, and fertile eggs are laid.

In the filariform infective stage the larva, by reason of its sheath, is able to withstand a certain amount of desiccation and extremes of temperature for a considerable period. There is evidence to show that the larvæ can exist alive in warm, damp soil under optimum conditions for upwards of

two years. The larvæ are markedly thermotropic, and on the application of a warm surface, such as the sole of the foot or any part of the body, they are immediately aroused to activity and attracted to that spot (*see also* p. 808).

The differentiation of the third stage ancylostome larvæ is given by Eisma as follows :

	Necator.	*Ancylostoma.*
ORAL CAPSULE.	[illegible] defined ; equally visible dorsally and ventrally.	Hardly visible ; more marked dorsally than ventrally.
TAIL.	Rather blunt.	Pointed.
ZONE OF CLOSING CELLS.	Leaves only a small space between œsophagus and intestine.	Leaves considerable space.

As a distinguishing feature between two ancylostomes, the striation of the sheath is indistinct in *A. duodenale*, very distinct in *A. braziliense*.

ŒSOPHAGOSTOMUM APIOSTOMUM (Willach, 1891)

This worm inhabits the cæcum and colon of monkeys in Africa, the Philippines and China. It is found in West Africa, especially Northern Nigeria. It is known to occur in the many

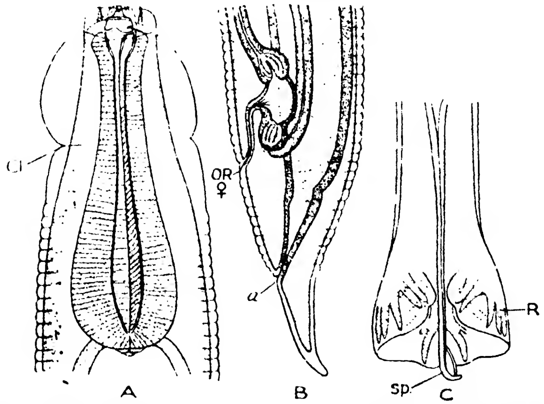


Fig. 252.—*Œsophagostomum apiostomum* (*brumpti*). (*Partly after Railliet and Henry.*)

A, Head, showing cuticular expansion and oral vestibule. B, Tail of female. C, Tail of male, showing copulatory bursa.

a., Anus ; *Cl.*, ventral cleft ; *OR.*, vaginal orifice ; *R.*, characteristic rays of bursa ; *Sp.*, spicule.

species of Old World monkeys. In Northern Nigeria it is found in about 4 per cent. of prisoners in the jails.

In both sexes there is an ovoid expansion of the cuticle at the anterior end, which is limited in front by a salient oral ring and posteriorly by a constriction which is especially marked on the ventral surface 200 μ distant from the oral vestibule ; this in turn is provided with a crown of 12 sharp, chitinous plates directed forwards and inwards. (Fig. 252.)

The *male* is 8–10 mm. in length by 0·35 mm. in breadth ; the copulatory bursa has a dorsal ray which bifurcates into two branches, forming a horse-shoe-shaped structure each limb gives off a short lateral horn near its base. (Fig. 252, c.)

The *female* is 10 mm. in length by 0.325 mm. in breadth. Posteriorly she terminates in a sharp point; the vulva is situated in the anterior half of the body.

The *eggs* are passed in an advanced stage of development, and measure 60 μ in length by 40 μ in breadth, and closely resemble those of ancylostoma.

The life-cycle of this worm is probably as follows: The larvæ (rhabditiform stage) are swallowed and pass undigested through the stomach and small intestine, and on arrival in the cæcum exsheath and invade the wall, where they cause nodule-formation.

These worms are found both free and encysted under the mucous membrane of the large gut, usually in the cæcum. In monkeys it produces a condition resembling *polyposis intestini.*

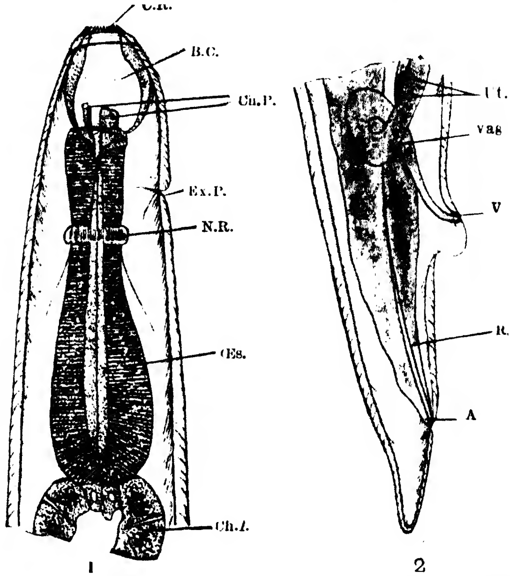


Fig. 253.—*Ternidens deminutus*, female. (*After Leiper.*)

1, Anterior extremity. 2, Posterior extremity. C.R., corona radiata. B.C., buccal cavity. Ch.P., chitinous plates; N.R., nerve-ring; Œs., œsophagus; Ch.I., chyle intest. Ut., uterus; Vag., vagina; V., vaginal opening; R., rectum; A., anus.

ŒSOPHAGOSTOMUM STEPHANOSTOMUM (Railliet and Henry, 1909)

This species, which was discovered by Foy in a West African native, is also a parasite of monkeys and the gorilla. In general characteristics it resembles the above, but the measurements for both sexes are nearly double the size. It has also been found by Joyeux in French Guinea and by Johnson (1933) in Northern Nigeria. The eggs in the fæces are liable to be mistaken for those of the ancylostome. This worm is common in the intestinal tract of monkeys, especially *Cercopithecus callitrichus.*

If the infection is severe the worms may give rise to dysenteric symptoms. The case described by Thomas in 1910 in a Brazilian with septic peritonitis was due to the subspecies *O. stephanostomum* var. *Thomasi.*

TERNIDENS DEMINUTUS (Railliet and Henry, 1905)

This parasite inhabits the large intestine of monkeys, *Macacus sinicus, M. cynomolgus Cercopithecus pygerythrus* and *Papio porcarius*, and has been found in man, being a not uncommon parasite of man in the Transvaal and in Nyasaland, but, unless it occurs in large numbers, it is of no pathological importance.

The worm resembles a female ancylostome in size, but the anterior extremity is not bent as in the hookworms, and the mouth-capsule opens terminally and has a corona of setæ. At the base of the large cup-like buccal capsule are three serrated teeth which guard the entrance to the œsophagus. These teeth are characteristic of the genus *Ternidens.* (Fig. 253.)

The *male* is 9·5 mm. long by 0·56 mm. broad. The dorsal ray of the copulatory bursa divides into two towards its distal extremity, and each of the branches formed again bifurcates. (Fig. 254.)

The *female* is 14–16 mm. in length and 0·73 mm. in breadth. The genital orifice is posterior and subterminal. The vagina is short and opens into two uterine tubes. The *eggs*, which resemble those of *N. americanus*, are delicate, transparent, and oval, measure 84 μ in length by 40 μ in breadth, and are passed in an advanced stage of segmentation. (Fig. 255.) The life-history has been partially worked out by Sandground (1931). A rhabditiform larva, 0.3 mm. in length with a flagellum-like tail, hatches out from the egg. The sheathed infective filariform larva is 0.6–0.7 mm. in length. The larva can withstand desiccation, reviving on the addition of water. It is thus equipped to withstand protracted periods of drought. These larvæ fail to penetrate the human skin.

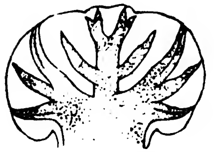


Fig. 254.—Bursa of *Ternidens deminutus*, ♂. (*After Brumpt.*)

Trichostrongylus colubriformis (Giles, 1892)

This nematode occurs not infrequently in the upper part of the small intestine, in India, Japan, Egypt and Central Africa. Originally described by Looss in man, it is normally a parasite of the sheep or goat; it is found frequently in Japan and Korea. By using the floatation technique in detection of the eggs in the fæces, Lane finds it is commoner in the fæces of ancylostome patients than has been supposed, and Chandler records it in 10 per cent. of cases in Assam. The females (Fig. 256A) greatly outnumber the males and measure 4–6·5 mm. In colour pale pink, the anterior extremity is attenuated. The vulva is situated in the posterior quarter of the body. The male (Fig. 256B) is 4–5 mm. in length by 0·07 mm. in breadth and is provided with a bilobed copulatory bursa and two spicules. This parasite does not occur in large numbers in man; the mouth is unarmed, and on this account, as well as of its small size, it does not give rise to any particular symptoms. The eggs (63 μ by 41 μ) are relatively large; they are oval, thin-shelled and contain a morula at oviposition. (Plate XXXIII, 15, p. 1025.) On account of their general resemblance they are apt to be mistaken in fæces for those of the ancylostome, but they are more translucent and smaller in size. When large numbers develop in the human intestine, they may produce a severe secondary anæmia. The Editor has not infrequently found the eggs of this parasite in the stools of lascars and other Indians, but in Europeans it is very rare; he has treated two cases from Kenya in husband and wife.

The eggs of this parasite hatch outside the body of the host and the rhabditiform larvæ metamorphose into the infective filariform type in six days, at 22 to 25° C. They enter the body either through the skin or *via* the mouth, following the same course of development as the ancylostome.

The Eastern form has been separated as *Trichostrongylus orientalis*.

A third species—*Trichostrongylus probolurus* (Railliet, 1896) occurs as a natural infection in the gazelle and the camel, and has also been found in man. Its life-history is similar to that already described. These worms can be expelled by carbon tetrachloride.

Strongyloides stercoralis (Bavay, 1876)

The parasitic form of this nematode lives in the submucous tissue of the small intestine.

It has an almost world-wide distribution, but is especially common in Brazil and Cochin-China.

Fig. 255.—Egg of *Ternidens deminutus*. (*After Blackie.*)

The parasitic form is generally considered to be a parthenogenetic female, 2·5 mm. long by 0·034 mm. broad (Fig. 257, *1*), but it is now claimed by Kreis (1932) that a parasitic male exists, and that it has a shorter, broader body than the female and the œsophagus conforms to the characteristic rhabditiform type. Later, two copulatory spicules and a gubernaculum became apparent. The fully adult parasite resembles the free-living male. It appears that this male, by a process known as *reversive metamorphosis*,

has lost its ability to penetrate the tissues and remains a lumen parasite. The body of the parasitic female tapers anteriorly and ends in a conical tail. The mouth has three small lips which give access to an œsophagus occupying a quarter of the length of the body. The vulva is in the posterior third of the body, and the prominent uterus contains 50 eggs measuring 50–58 μ long by 30–34 μ broad. The eggs are laid in the lumen of the bowel in a very advanced stage of development. Hatching almost immediately, they give rise to rhabditiform embryos which measure 0·2–0·3 mm. in length by 0·013 mm. in breadth ; these possess the characteristic double-bulbed œsophagus, and may easily be confused with the rhabditiform stage of *Ancylostoma* or *Necator* (Figs. 257, *2*, and 251). In this stage the embryos are passed in the fæces. In three to five days the larvæ develop into free-living male and female forms.

Both sexes possess a remarkable rhabditiform or double-bulbed muscular

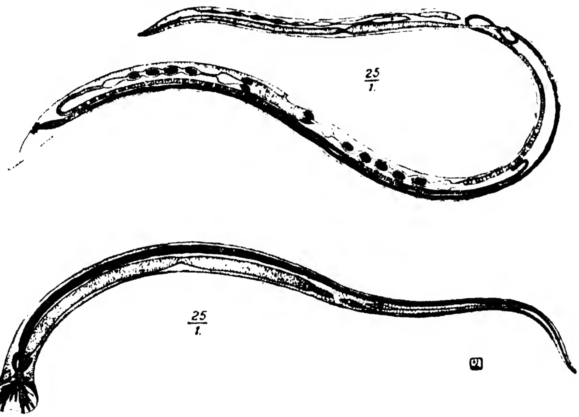


Fig. 256.—Trichostrongylus colubriformis. A, female ; B, male. × 25.

œsophagus. The *male* free-living form measures 0·7 mm. in length by 0·035 mm. (Fig. 257, *3*). The tail is curved ventrally, and two spicules and an accessory piece are present. The *female* free-living form measures 1 mm. in length by 0·05 mm. in breadth. The vulva is situated a little behind the middle of the body ; the uterus usually contains several thin-shelled eggs, 70 μ in length by 40 μ in breadth (Fig. 257, *4*). Copulation between the sexes takes place in the fæces, and, as a result, rhabditiform embryos are produced which are indistinguishable from the rhabditiform embryos derived from the parasitic female.

These rhabditiform embryos, after three or four days, develop into long filariform larvæ which are the infective stage of the parasite and which may re-enter the definitive host *via* the skin or buccal mucosa in the same manner as the embryos of *Ancylostoma* and *Necator* gain entrance into their host. The filariform larvæ find their way into the small intestine and develop there into the parasitic, parthenogenetic female form. In certain circum-

stances, e.g. unsuitable climatic conditions, the sexual phase which takes place in the fæces may be omitted, and the rhabditiform embryos produced by the parthenogenetic female may directly develop into the filariform embryos which are capable of infecting the definitive host. (Fig. 257, *5*.)

A significant discovery has been made that the directness or indirectness during the free-living phase is contingent solely upon environmental factors.

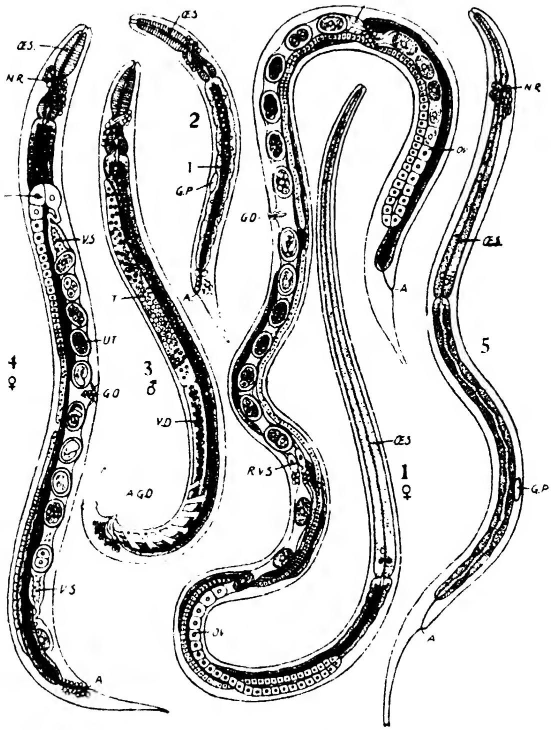


Fig. 257.—Life-history of *Strongyloides stercoralis.* × 30. (*After Looss.*)

1, (Parasitic) parthenogenetic female; 2, rhabditiform embryo; 3, fully-grown male; 4, fully-grown female; 5, fully-developed filariform larva.

A., anus; A.G.O., combined anus and genital pore; G.O., genital opening; G.P., primitive genital organs; I., intestine; N.R., nerve-ring; ŒS., œsophagus; OV., ovary; R.V.S., rudimentary vesicula seminalis; T., testis; UT., uterus; V.D., vas deferens; V.S., vesicula seminalis.

Optimum conditions produce continuous free-living rhabditiform generations, while unfavourable ones shorten free-living developmental metamorphosis.

The filariform stage of *Strongyloides* is liable to be confused with that of the same stage of *Ancylostoma* or *Necator*, but microscopical examination will reveal the fact that, whereas in the former the œsophagus is about half the length of the body, in both the latter it occupies but a quarter (*see* Fig. 257, *5*).

Subjoined is a summary of the life-history of *S. stercoralis*:

Evolution of S. stercoralis.—Parasitic intestinal form gives rise to—

which, hatching in the intestinal canal of man, give rise to—

First rhabditiform larvæ in the fæces. At high atmospheric temperature these larvæ give rise either to *infective* or to *sexual* forms, which copulate, and the females lay

Eggs,

from which emerge—

Second rhabditiform larvæ. These moult and give rise to filariform larvæ, which enter man either by penetrating the skin or through the mouth, and develop within two weeks into—

The (*parthenogenetic*) *parasitic female* in the small intestine.

Pathogenesis and treatment.—This parasite must undoubtedly produce considerable irritation of the bowel, which may give rise to diarrhœa. Hinman claims that it gives rise to vague abdominal pain and flatulency, and that the infection is usually found in males from twenty to forty years of age.

It is usually present in large numbers, and has been found coiled up in the intestinal follicles. The larvæ, after entering the skin, pursue a migration through the lungs and œsophagus similar to that of *Ancylostoma* and of *Necator*. Faust states that gentian violet acts as a parasiticide when it reaches the living female in sufficient concentration. It is given in enteric-coated tablets.

Fülleborn demonstrated that in persons infected with *S. stercoralis* a supersensitization to the antigens of this parasite exists. Itchy urticarial wheals are produced at the site of entry of further infecting larvæ in these persons, or even by rubbing into the skin dried extracts of strongyloides larvæ.

The prophylaxis is the same as that for *Ancylostoma*.

Enterobius vermicularis (Linn., 1758)
Threadworm (Pinworm)

Synonym.—*Oxyuris vermicularis.*

This worm lives in the upper part of the large intestine, especially the cæcum; occasionally invades the female genital organs and bladder; and more rarely occurs in the ear and nose. It is found all over the world.

These worms are small and white in colour. The mouth is surrounded by a cuticular expansion; the œsophagus in both sexes is provided with an extra bulb. (Fig. 258.)

The *male* (Fig. 258, B) is much smaller than the female, and is relatively uncommon. It measures 2·5 mm. in length; the posterior third is curved spirally. The caudal extremity is blunt, and possesses six sensory papillæ. A single spicule is present, and measures 70 μ in length. (Fig. 258, C.)

The *female* measures 9–12 mm. in length and has a long pointed tail. The anus is situated 2 mm. from the posterior extremity; the vulva, transverse and slit-like, is situated in the anterior fourth of the body (Fig. 258, A).

The eggs measure 50–54 μ in length and 20–27 μ in breadth. They have a characteristic shape, being flattened on one side. There are two shells: the outer is thick and transparent; the inner thin, and containing a more or less fully-formed embryo. (Plate XXXIII, *19*, facing p. 1030.)

The fertilized females migrate out of the anus and deposit their eggs in the natal folds. After a few hours have elapsed the embryos develop

rapidly and attain a length of 140–150 μ. At this stage the eggs are ingested, being usually carried by the fingers to the mouth, and on coming in contact with the digestive juices they hatch. The larvæ thus liberated pass after two moults from the small into the large intestine, where they become mature. The duration of the cycle is two weeks.

Mature worms are capable of penetrating the mucosa and of encysting in the submucosa of the small intestine or appendix, where they may cause inflammation. According to Battaglia, they may be the exciting cause of appendicitis in children, and in 2 per cent. of cases they have been found in this organ removed at operation. There is no marked eosinophilia in this infection. As there is no multiplication of parasites within the body, the number infecting the host is determined by the number of ova swallowed. Nasal itching may constitute a sign of the infection. The ova are deposited in enormous numbers around the anal region. Dozens of eggs can be recovered from beneath the finger-nails, and ova can be obtained from the washings of garments (Blacklock). Familial infections are common.

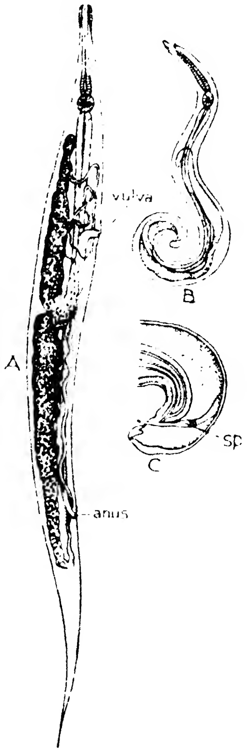


Fig. 258.—*Enterobius vermicularis.* × 12. (*After Leuckart, in Brumpt's "Précis de Parasitologie."*)

Lentze believes that the ova can be inhaled through the nose at some distance from infected garments. The diagnosis of oxyuriasis is sometimes difficult unless the worms are seen. The eggs may be found in the fæces. Hall has devised a cellophane sprayer known as the "N.I.H. swab," by which it is possible to obtain the eggs from the skin-surface of the perineum.

Treatment.—Oxyuriasis is often, especially in adults, an extremely difficult condition to treat. General measures, such as the wearing of sleeping-drawers of strong cotton and cotton gloves at night, the paring of the finger-nails, washing the hands carefully after defæcation, must be adopted. To prevent itching of the anus and to assist in prevention of the re-infection the anus should be smeared at night-time with some mercurial ointment, as the ung. hydrarg. ammon. B.P. Oxyuriasis is one of the commonest causes of *pruritis ani.* The itching usually ceases sometime before morning (MacArthur).

The worms are expelled per rectum by means of quassia; the rectum should first be evacuated by a hot-water enema or salt-and-water enema (one tablespoonful of salt to half a pint). After the bowel has been emptied, the infusion of quassia, diluted 1 : 40, is injected slowly per rectum, and the foot of the bed raised so as to allow it to percolate through the bowel. *Beta-naphthol*, 40 grains in ½ ounce of castor oil or, better still, in cachets, may be tried. *Tetrachlorethylene,* given by the mouth at the rate of 0·1 c.c. for each year of age, is recommended by Wright and Gordon. It should not

be given with magnesium sulphate, but with the citrate, which may be exhibited at night and followed next morning by an enema containing 1 c.c. of tetrachlorethylene in coconut-oil emulsion in a litre of water. Hexylresorcinol in keratin-coated capsules, in 1-grm. doses for an adult, may be given for a considerable period, as in ancylostomiasis, and is fairly effective (*see* p. 817). The Editor has found carbon tetrachloride treatment, alone or combined with oil of chenopodium, most effective, but rather toxic for children. Gentian violet is said to be efficient. The course advised is two periods of eight days, with an interval between of seven. The dose for adults is two "enteric-coated" tablets, each containing ½ grm. (7·5 gr.) of gentian violet, given three times daily before meals. For those under fifteen years of age it is one cgm. (1½ gr.) three times daily.

"Butolan," p-benzylphenol carbamin acidester (Bayer), given by the mouth in doses of 0·5 grm. three times daily for an adult, and persisted in for a week, or half that quantity for children under ten years of age, is sometimes effective. Oxylax, or *tubera jalapæ* (dihydroxyphtalophenol), in chocolate-coated tablets containing 0·15 grm., in the dose of one tablet daily for four weeks, is said to be effective in expelling the worms. Garlic used as an infusion has a reputation. This should be prepared by boiling the small roots in a litre of water for one hour, and should be injected per rectum. A diet consisting to a great extent of raw carrots is an old-fashioned remedy, and is efficacious in analogous infections of monkeys and other lower animals.

Trichuris trichiura (Linn, 1771).

Whipworm (Fig. 259).

Synonym.—*Trichocephalus dispar.*

This worm inhabits the large intestine, especially the cæcum. It is said to be identical with a species found in the pig. It is cosmopolitan in distribution.

These worms are greyish-white or slightly-pink in colour.

The *male* is 30–45 mm. in length; the anterior attenuated portion, which contains the simple cellular œsophagus, is half as long again as the thicker posterior body portion. The caudal extremity is curved ventrally, and there is a single spicule enclosed in a sheath which itself is closely studded with spines. (Fig. 259, *3.*)

The *female* is 30–50 mm. in length, while the anterior attenuated end is twice as long as the posterior. The *eggs*, of a characteristic barrel shape, are brown in colour and measure 50 μ in length by 22 μ in breadth. (Plate XXXIII, *18*, facing p. 1030.)

On leaving the body the eggs are unsegmented and the contained embryo develops but slowly, attaining its full length in 6–12 months. Owing to its thick shell, it can withstand a low temperature. The embryos can live, without developing any further, apparently for as long a period as five years. Development is direct; once ingested, the larvæ attain maturity within a month. The egg-shell is digested in the intestinal juices and the larva passes through to the cæcum or adjacent region of the bowel, attaches itself to the intestinal wall, and grows into an adult worm.

The worm lives chiefly in the cæcum. In many countries it is present in more than half the population. It maintains its position by transfixing, pin-fashion, with its long slender neck, a superficial fold of the mucous

membrane. Wichmann claims to have shown, by serial sections of the cæcum at sites where the parasites were fixed, that it is merely embedded in the mucus between the intestinal villi. According to Powell, the females very much preponderate, the proportion to males being as 466 to 1. Except that the practitioner should be familiar with the appearance of its eggs in the stool (Plate XXXIII, *18*), so that he may distinguish them from those of *Ascaris*, of *Ancylostoma*, and of other parasites, the presence of *T. trichiura* is of no practical moment. So far as known, it gives rise to no serious pathological lesion. This worm is difficult to expel. A certain number may be

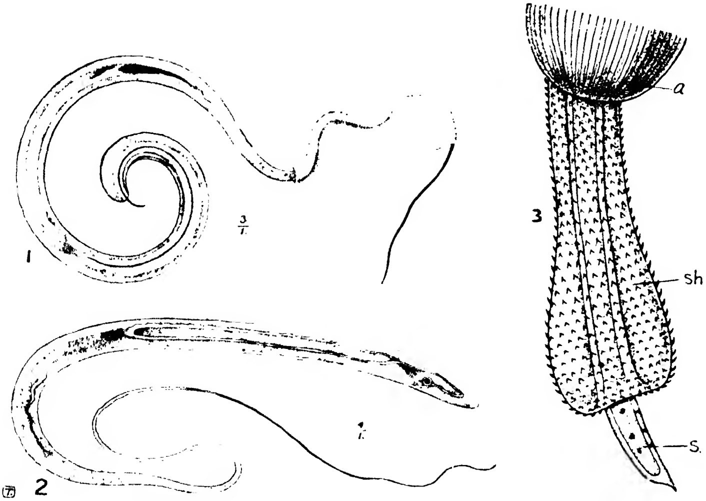


Fig. 259.—*Trichuris trichiura.* × 3. (*After Brumpt.*)
1, Male, partly embedded in the mucous membrane of the intestine; 2, female: 3, copulatory apparatus, greatly magnified. *a*, Posterior extremity of body; *s.*, spicule; *sh.*, sheath.

removed by the carbon tetrachloride and oil of chenopodium method (p. 816), and it has been stated by Vazquez Pausa that a mixture of ferri et ammon. cit. 2 grm. with 0·4 grm. mang. cit. and 0·1 grm. cupr. cit. is a cure for these worms.

Capyllaria hepatica (Bancroft, 1893) (Hall, 1916)

Synonyms.—*Trichocephalus hepaticus; Hepaticola hepatica.*

This parasite belongs to the family Trichuridæ, and is closely allied to *T. trichiura*; it is normally a parasite of the rat, infecting the liver, where it deposits masses of characteristic trichuris-like eggs in the substance of that organ. The life-cycle, like that of Trichuris, is direct, requiring only a single host.

A case of this infection has been reported by Dive and MacArthur as occurring in a British soldier in India. Death took place from septic pneumonia secondary to an abscess of the liver caused by accumulations of adult worms, characteristic masses of eggs of *C. hepatica* being found in the liver-substance. The eggs are not usually found in the fæces.

Trichinella spiralis (Owen, 1835)

This worm is found in the muscles, especially the laryngeal, the diaphragm and the intercostals.

Originally discovered by Hilton, a demonstrator at Guy's Hospital, in 1833, it was "rediscovered" by Paget in 1835, who referred it to R. Owen in the same year. Herbst in 1851 first undertook feeding experiments, which proved that the larvæ developed into the adult form, and this was fully confirmed by Leuckart in 1860.

In Europe, *Trichinella* was formerly common in Germany until the most stringent prophylactic measures were taken. In America it is still very common; in Boston, for instance, it is estimated that in the municipal slaughter-houses 5 per cent. of the pigs are infected. In Asia it has been found in China and India: and epidemics have been reported in Syria from eating the flesh of naturally infected wild boars. In Africa it is found in Algeria and in the East African Protectorates. It has been reported occasionally from Australia. Pigs become infected most frequently by eating garbage from abattoirs.

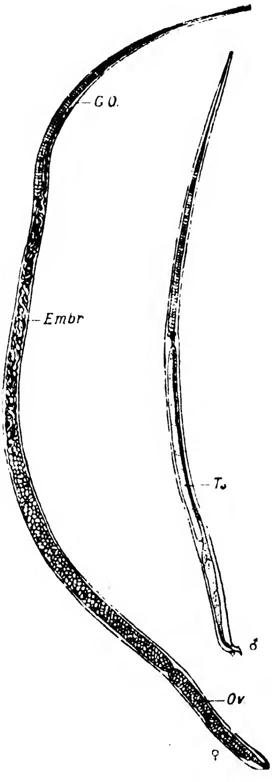


Fig. 260.—*Trichinella spiralis*, female and male. × 45. (*After Brumpt.*)

G.O., Genital opening; *Embr.*, embryos; *Ov.*, ovary; *T.*, testis.

Trichinella is a white worm just visible to the naked eye. The *male* (Fig. 260) is 1·6 mm. in length by 0·04 mm. in breadth; the cloaca, situated posteriorly between two caudal appendages, is provided with two pairs of papillæ. The *female* (Fig. 260) is viviparous, 3–4 mm. in length by 0·06 mm. in breadth; the vulva is situated in the anterior fifth, the posterior half of the body being occupied by the ovary, the anterior by a much-coiled uterine tube. The anus is terminal.

The worms inhabit the small intestine. The young, which the female emits, migrate into the muscles, where they encyst. In a natural state the pig, wild boar, and rat act as hosts in addition to man, but the majority of animals, even lizards, are capable of being infected under artificial conditions. Birds, however, are refractory.

Infection of a fresh host is brought about by ingestion of raw flesh of a trichinosed animal—that is, one in whose muscles the larval trichinellæ are encysted. Man becomes diseased in this manner by eating uncooked pork. The development of adults from larvæ would appear to take place with astounding rapidity, and in as short a period as forty-eight hours after ingestion, it is said that mature male and female worms can be found in the intestine. After a further twenty-four hours, embryos have already appeared in the uterus of the fertilized female.

The eggs, measuring 20 μ, are found in the upper portion of the uterus, but soon the contained embryo breaks loose and lives free in the uterine cavity. The living embryos are voided into the lumen of the intestine, and measure 100 μ in length by 6 μ in breadth. Travelling independently *via* the lymphatics, and to some extent also *via* the venous channel, and guided

by a mysterious instinct, these embryos pierce the coats of the containing vessels and encyst in striated muscular tissues, especially that of the diaphragm, the intercostal and laryngeal muscles, and those of the neck and eye, especially at their tendinous insertions. The cysts themselves are oval in shape, the cyst wall being formed by the reaction of the tissues. Fig. (261.)

The objective symptoms may resemble those of cholera, or possibly those of dysentery, with passage of blood-stained stools, associated with hyperpyrexia (temperature 104°–106° F.). During the migration of the larvæ through the tissues typhoidal symptoms predominate, with remittent temperature and slow muttering delirium, merging into rheumatic muscular pains, difficulty in mastication, deglutition, and respiration. Three weeks after infection, while the embryos are encysting in the muscles, a profound cachexia, probably due to absorption of the toxins from the larval trichinellæ, supervenes. Œdema of the face, abdomen, and legs is often noted. Together with this there are mental apathy, intense pruritis, and sometimes skin eruptions. Death may take place in the sixth or seventh week, from exhaustion or from pulmonary complications. In the cases which survive, the fever gradually resolves, but muscular pains of varied intensity persist.

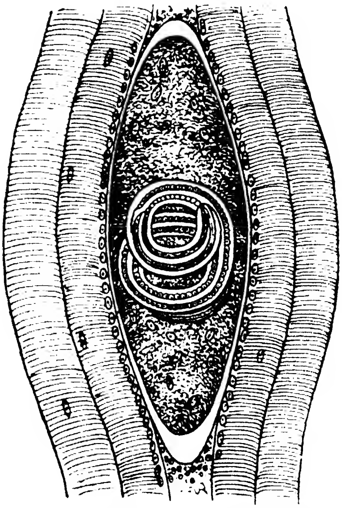


Fig. 261.—Encysted larva of *Trichinella spiralis*, fifteen days after entering muscle. × 300. (*After Claus, in Brumpt's "Précis de Parasitologie."*)

Diagnosis. — The early intestinal symptoms must not be confused with ptomaine poisoning, cholera, or dysentery. The debility, delirium, and remittent pyrexia may suggest typhoid; the œdema may be mistaken for that of nephritis, though, of course, the urine is free from albumin. From these conditions trichinosis may be differentiated by the high eosinophilia of the blood, by a negative Widal reaction, and by the discovery of the adult worms and, in the later stages of the disease, of the embryos in the fæces. In the more chronic rheumatoid stages the characteristic encysted larvæ can be recognized under the microscope in a small portion of muscular tissue removed for this purpose.

It has been found, in England as well as in America, that quite a large number of cases of subclinical trichiniasis still exist. In America it is estimated, by employing the method of digesting the portion of excised muscle in artificial gastric juice in order to demonstrate the larvæ, that 20 per cent. of the population are infected. Van Someren has, by the same method, shown that 1 per cent. of the population in England is in the same condition.

Bachman (1928) showed that positive precipitin tests could be obtained by using extracts of the isolated parasite, but the reaction usually becomes

positive too late to be of practical value. The intradermal reaction consists of injecting an antigen prepared from artificially-infected rabbit muscle. Two types of reaction are produced: (1) immediate, characterized by the formation of a papule, and (2) delayed, which reaches its maximum twenty-four hours after injection. Most American workers find that a 1 : 10,000 dilution of antigen in Coca's solution gives the best results two to three weeks after infection.

Wuchereria bancrofti (Cobbold, 1877; Seurat, 1921)

Synonym.—*Filaria bancrofti* (Cobbold, 1877).

This parasite lives in the lymphatic vessels and glands of man.

It has a wide tropical and subtropical distribution, and has been found as far north as Spain in Europe, and as far south as Brisbane, Australia.

W. bancrofti is a thread-like, white worm found in lymphatic glands and vessels. The sexes are generally coiled together, and can only with difficulty be separated. (Figs. 129, 130, p. 745.)

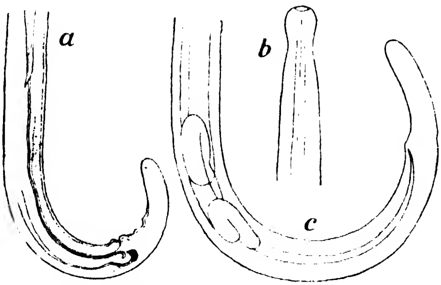


Fig. 262.—Parental forms of *W. bancrofti*. Magnified.
a, Tail of male; *b*, head and neck; *c*, tail of female.

The *male* is 40 mm. in length by 0·1 mm. in breadth, and generally lies coiled up with a markedly corkscrew-like tail. Two spicules of unequal size and an accessory piece are present. The larger spicule, 500 μ in length, has a short, thick proximal portion, and a long whip-like distal portion ending with a hook. The shorter spicule is grooved on its ventral aspect, and measures 200 μ in length. The accessory piece is crescentic. There are 15 pairs of minute caudal papillæ. (Fig. 262, *a*.)

The *female* measures 65–100 mm. in length by 0·20–0·28 mm. in breadth; the genital opening is situated 0·6–1·3 mm. from the anterior end, which is tapering and ends in a rounded swelling. The head is provided with two rows of small sessile papillæ; the oral aperture leads to a cylindrical œsophagus. The mid-intestine is a tube of one-third to one-fifth of the diameter and opens into a short rectum posteriorly. The caudal extremity is narrow, but abruptly rounded. (Fig. 262, *c*.) The vulva opens 0·8 mm. behind the anterior extremity, and the swollen vagina is about 0·25 mm. in length and leads into a uterus, which shortly divides into two branches. These tubules are much coiled and occupy the greater portion of the body; their diameter being about three times that of the mid-intestine. (Fig. 263.) The two ovaries and their associated ducts extend to within 1 mm. of the caudal extremity. The eggs in the upper part of the uterus contain well-formed embryos enclosed

in a membrane which subsequently becomes the sheath of the living microfilaria. (Fig. 264.) These embryos emitted by the viviparous female find their way by the lymphatics into the blood-stream and are taken up by various species of mosquito of the genera *Culex*, *Aëdes* (*Stegomyia*), and *Anopheles*, in whose thoracic muscles they develop.

The embryos of all the Filaridæ are generally known as microfilariæ.

Description of embryo (microfilaria).—When examined with a low power, the embryo appears to be structureless; with a high power a certain amount of structure can, on close scrutiny, be made out. In the first place, it can be seen that the entire embryo is enclosed in an exceedingly delicate, limp, structureless sac, in which it moves backwards and forwards. This sac, or "sheath," as it is generally called, although closely applied to the body, is considerably longer than the enclosed embryo; so that that part of the sac which for the time being is not occupied is collapsed and trails after the head, or tail, or both, as the case may be. It can be seen also that about the posterior part of the middle third of the parasite there is what appears to be an irregular aggregation of granular material which, by suitable staining, can be shown to be a viscus of some sort (*Innenkörper*). Further, if a high power be used, a closely set, very delicate transverse striation can be detected in the musculo-cutaneous layer throughout the entire length of the embryo. Besides this, if carefully looked for at a point about one-fifth of the entire length of the organism backwards from the head end, a shining, triangular V-shaped patch is always visible, which is brought out by very light staining with dilute hæmatoxylin. The dye brings out yet another spot similar to the preceding, though very much smaller; this second spot is situated a short distance from the end of the tail. The former has been designated the V-spot, the latter the tail-spot. These spots are connected with development, the V-spot being the rudiment of the future water-vascular system: the tail-spot that of the anus or cloaca and terminal part of the alimentary canal. (Fig. 269, *1*.) Staining with hæmatoxylin also shows that the body of the embryo is composed of a column of closely packed, exceedingly minute cells enclosed in a transversely striated musculo-cutaneous cylinder. Low has pointed out that the break seen in stained specimens in the central column of nuclei occurs at a point slightly anterior to the V-spot, which is the position of the nerve-ring. The sheath of the microfilaria represents the chorionic envelope of the ovum, and is stretched out as the embryo uncoils itself on leaving the parental uterus. (Fig. 264.) Knott has shown that these microfilariæ have great difficulty in passing through the peripheral capillaries, and that they are less active in day than in night blood, and suggested that in this observation may lie part of the explanation of nocturnal periodicity. Drinker and his colleagues have shown that the sheathed

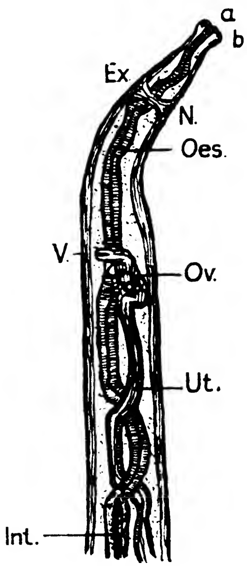


Fig. 263.—Diagram of head of *W. bancrofti* ♀. × 50.
a., mouth; b., circumoral papillæ Ex., excretory pore; Int., Intestine; N., nerve-ring; Oes., œsophagus; V., vulva; Ov., oviduct; Ut., uterus.

microfilaria is capable, not only of movement, but of actual transit from place to place.

When the movements of the living microfilariæ have almost ceased, by careful focusing it can be seen that the head end is constantly being covered and uncovered by a very delicate prepuce; moreover, one can sometimes see a short fang of extreme tenuity, based apparently on a highly retractile granule, suddenly shot out from the uncovered extreme cephalic end, and as suddenly retracted (Fig. 133, p. 748), and in a fresh blood preparation it can be seen disturbing the red cells at some distance away.

Filarial periodicity.—The microfilariæ of this species exhibit what is known as nocturnal periodicity—that is to say, they are present in the peripheral blood in larger numbers during the night than during the day. In the West Indies, India, and China the maximum concentration of embryos in the peripheral blood occurs between 10 p.m. and 2 a.m. It is thought that this nocturnal periodicity is an adaptation to the habits of the intermediary host, which in this case is a night-biting mosquito, *Culex fatigans*.

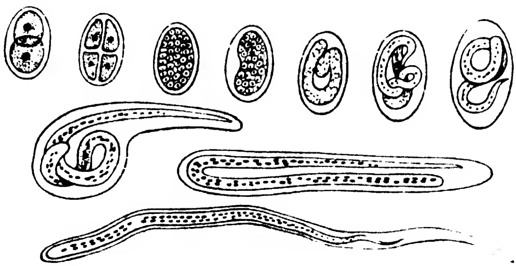


Fig. 264.—Evolution of sheathed microfilaria from ovum in uterus of parent worm. The later stages may occasionally take place after emission from vagina. *(Partly after Penel.)*

The mechanism by which this periodicity is produced has never been satisfactorily explained. In the strictly nocturnal variety, the numbers of circulatory embryos are influenced by the act of sleeping, and respond instantly, as has been shown by the Editor and Low. By reversing the hours of sleeping and waking the periodicity can within the space of three days be reversed. Recent observations have shown that *Dirofilaria immitis* of the dog, and the microfilariæ of birds, especially of the American crow (*Corvus brachyrhynchos*), maintain a nocturnal periodicity, but are very sensitive to darkness and light. This bird is found to be a suitable experimental creature, in which the host activity is sharply related to the behaviour of the parasite, and one in which also reversal of nocturnal periodicity is easily accomplished (Boughton, Byrd, and Lund, 1938).

On the other hand, the microfilariæ which are found in the blood of the inhabitants of some of the Pacific islands (e.g. Fiji, Samoa, Tokelau, Wallis, Ellice Islands, Philippines, and Tahiti), although at present considered on morphological grounds to be identical with the microfilariæ of *W. bancrofti*, do not exhibit this nocturnal periodicity, but appear in the blood-stream in irregular numbers during the day- and night-time (non-periodic). As this microfilaria has been shown by the Editor to develop in a purely diurnal mosquito intermediary, namely *Aëdes variegatus* (*Stegomyia pseudoscutellaris*),

it is considered by some to be specifically different from *W. bancrofti*, which occurs in other parts of the tropics. As far as is at present known, the adults of the non-periodic microfilaria are morphologically identical with *W. bancrofti*. It is possible that the former variety of *W. bancrofti* represents a species distinct in the biological sense, but Africa, Garcia and others have shown, in the Philippines at any rate, that the two filariæ, periodic and non-periodic, exist side by side.

Life-history.—Further development of the embryo into the stage known as the larval filaria takes place in the thorax of various species of mosquito. Within an hour and a half of entering the mosquito's stomach, the microfilariæ cast their sheaths, and within twenty-four hours the majority have entered the thorax, where they come to lie between the wing muscles. Within the next two days the larval filaria increases greatly in girth, and the posterior V-spot now enlarges; and shortly afterwards the anterior V-spot, or excretory pore, similarly becomes much more prominent. By rapid nuclear proliferation the larval filaria assumes a squat "sausage"

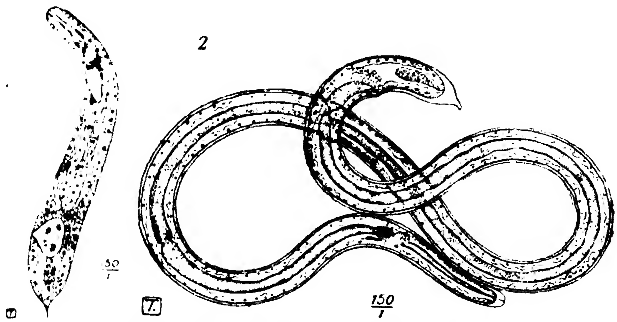


Fig. 265. -Stages of larval form of *W. bancrofti*, from thoracic muscles of *Culex fatigans*. × 150. (*After Looss.*)

form (Fig. 265, *1*); the tail now shrinks and is absorbed. The mouth and œsophagus become apparent from the fifth day onwards, and at the same time the posterior V-spot now becomes transformed into the anus. (Fig. 265, *2*.)

The œsophagus at this stage has a bulbar enlargement at the first and second fourths of the alimentary canal at a time when the larva is 0·5 mm. in length. The larva, now elongated and worm-like, commences to move about the thorax with sluggish undulating movements. The alimentary canal being complete, the caudal papillæ appear; they are three in number, and subterminal, and their function is probably to assist the filaria to progress, and thereby facilitate its subsequent penetration of the skin. Towards the tenth day, in the most favourable circumstances, the snake-like larval filaria, now measuring 1·4 mm., travels forward through the thorax into the head, where it lies coiled up ready to enter the proboscis sheath of the mosquito. It may also be occasionally found in the abdominal cavity or legs of the insect. (Fig. 266.) During the period of development of the filaria in the mosquito two or more ecdyses take place.

O'Connor and Beatty have made some original observations which differ in detail from the generally accepted account. At the end of ten hours after

the infective feed, the embryos begin to collect at the anterior end of the stomach of the mosquito. Shortly afterwards they enter the anterior cylindrical portion of the midgut. This forward transportation goes on, partly as the result of reversed peristalsis, till they are distributed over the whole of the cylinder; at the end of sixteen hours they have collected to form a writhing mass just behind the valve which stops progress into the foregut. These workers have also shown, what had been surmised originally by Manson and others, that the mosquito's proboscis exerts some positive chemiotactic effect upon the microfilariæ; thus *Culex fatigans* can abstract

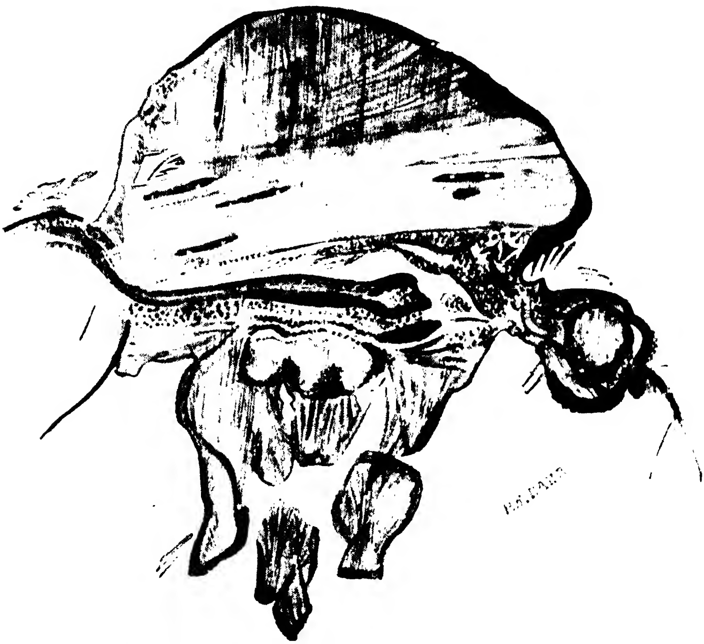


Fig. 266.—Section of thoracic muscles of *Aëdes variegatus*: second day after feeding on filariated patient. (*Orig.*)

more embryos than can be obtained in the same quantity of blood by mechanical means. A mosquito abstracts about 1 cu. mm. of blood at each feed and thus the concentration of embryos is apparently ten-fold.

Under conditions of high temperature and moisture the complete cycle takes 10–14 days, but development may be retarded by cold to six weeks or more. Sometimes the larva, during development, dies in the thoracic muscles and becomes encased in chitin, producing the peculiar structure seen in Fig. 137, p. 753. When the infected mosquito begins to bite another individual man, the larvæ, attracted by the warmth of the skin, break their way through the terminal portion of the proboscis sheath of the insect, known as Dutton's membrane, and, wriggling out on to the skin, rapidly penetrate it near the seat of puncture caused by the stylets of the mosquito (Fig. 267).

Formerly, it was supposed that the mosquito actually injected the larval filaria into the tissues of the victim, but this has been disproved.

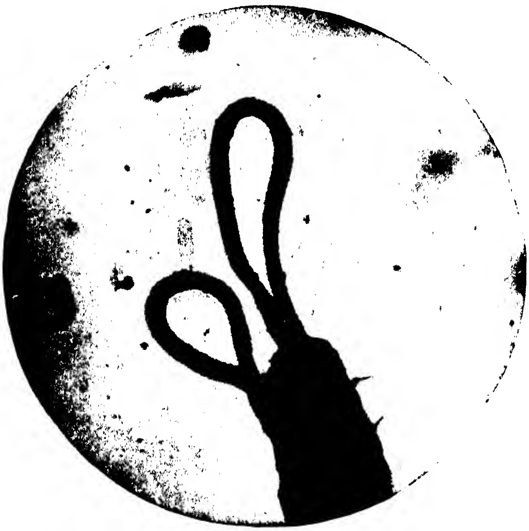


Fig. 267.—Larval filaria emerging from proboscis of *Aëdes variegatus*. (*Orig.*)

Complete development of the larval *Wüchereria bancrofti* has been observed in the following species of mosquito :

(1) *Culex fatigans*. West Indies, India, Philippines and parts of the Pacific.
(2) *Culex pipiens*. China.
(3) *Culex habilitator*. St. Croix, West Indies.
(4) *Culex quinquefasciatus*. Celebes, Dutch East Indies.
(5) *Culex alis*. Celebes, Dutch East Indies.
(6) *Culex whitmorei*. Celebes, Dutch East Indies.
(7) *Culex vishnui*. Celebes, Dutch East Indies.
(8) *Culex annulirostris*. Celebes, Dutch East Indies.
(9) *Mansonioides annulifera*. South India (Iyengar).
(10) *Aëdes variegatus*, Syn. *Stegomyia pseudoscutellaris*. Pacific Islands. (Manson-Bahr).
(11) *Aëdes* (*Finlaya*) *togoi*. Japan.
(12) *Aëdes chemulpœnsis*. Japan.
(13) *Tæniorhynchus* (*Mansonioides*) *africanus*. Central Africa.
(14) *Anopheles rossi*. India.
(15) *Anopheles nigerrimus*. South India.
(16) *Anopheles gambiæ* (*costalis*). West Africa.
(17) *Anopheles algeriensis*. Tunis.
(18) *Anopheles annictus*. Queensland.
(19) *Anopheles albimanus*. St. Croix, West Indies.
(20) *Anopheles barbirostris*. Celebes and New Guinea.

(21) *Anopheles aconitus.* Celebes, Dutch East Indies.
(22) *Anopheles annulirostris.* Celebes, Dutch East Indies.
(23) *Anopheles subpictus.* South India (Iyengar).
(24) *Anopheles vagus.* South India (Iyengar).

Twenty-two species have been listed in which partial development has been observed.

FILARIA MALAYI

The embryo (microfilaria) only is known and is the common form of filaria in Malaya, Dutch East Indies, Central India, Ceylon, Southern China and Indo-China. It has not yet been found in Africa, America, Australia or the Pacific Islands. The zoological affinities of the parasite cannot be determined until the adult form has been discovered and this should not be difficult to obtain. Possibly the filaria recently described by Rishworth and Maplestone, and which resembles *L. loa*, may be the parental form (Fig. 268).

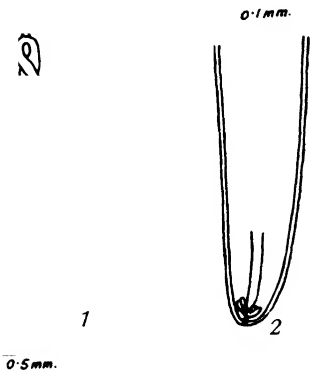


Fig. 268. — Diagrams of *Filaria malayi* (*Loa inquirenda*) from Bombay.

1 Anterior extremity, showing vulva and vagina; 2, posterior extremity.

Microfilaria malayi was first obtained by Lichtenstein from natives of Celebes, and was studied by Brug. The embryo has a nocturnal periodicity like that of *Wüchereria bancrofti*. This has been definitely established by Brug in Celebes, Poynton and Hodgkin in Malaya, and Gaillard in Indo-China, as well as in Hunan (Liu), and Chekiang, South China (Feng and Yao). All are agreed that the periodicity is not absolute as in the case of *W. bancrofti*. The embryo measures 200–250 μ in length by 5–6 μ in breadth. The chief points of distinction are the presence of an elongated nucleus at the tip of the tail and absence of one in the cephalic space.

The following table summarizes the main points of distinction between microfilaria malayi and microfilaria bancrofti:

Microfilaria malayi (Fig. 269, *2*).	*Microfilaria bancrofti* (Fig. 269, *1*).
It is often found closely folded with head close to tail, and is irregularly disposed, for besides major curves, minor angulations are typical.	Usually seen lying with head and tail well separated, and commonly shows three or four major curves of graceful appearance.
The nuclei are blurred and intermingled so that they cannot be easily counted.	The nuclei are well defined and spaced and can be easily counted.
The tail tapers to a fine point, continued as a fine thread. There is typically one nucleus at the extremity of the tapered portion and two in the terminal thread.	The tail tapers to a point and the terminal portion contains no nuclei.

Microfilaria malayi (Fig. 269, 2).

The anal pore is clear space about 40 μ from the tail end.

The cephalic space is twice as long as broad.

The excretory pore and cell are separated.

Microfilaria bancrofti (Fig. 269, 1).

The cephalic space is as long as it is broad.

The excretory pore and cell are close together and a thread of protoplasm runs posteriorly from the latter.

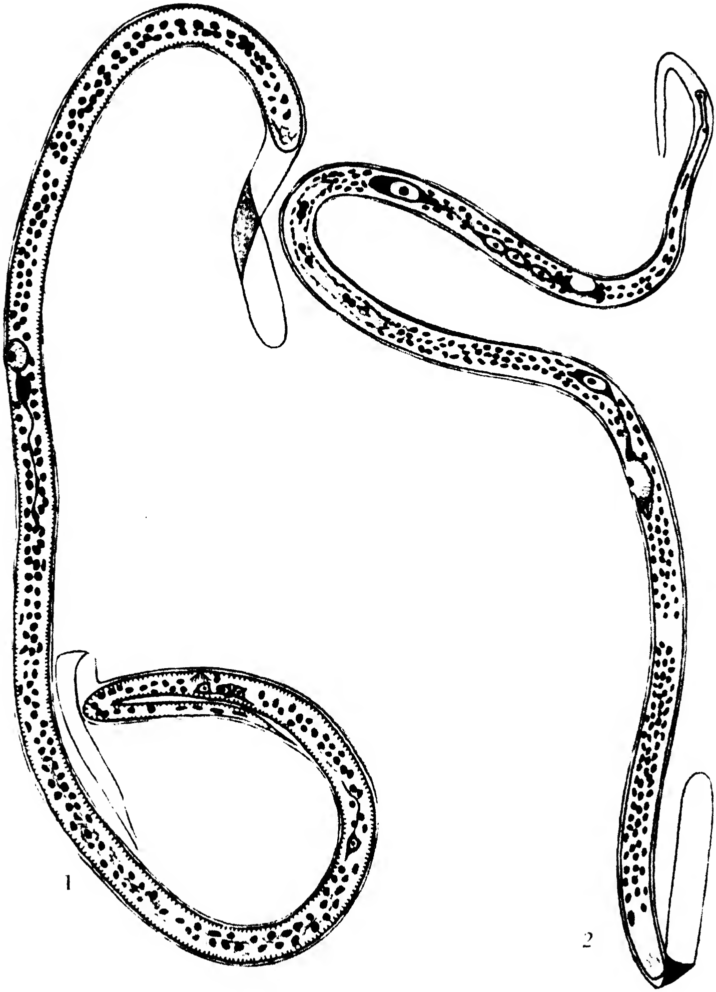


Fig. 269.—(1) Microfilaria bancrofti ; (2) Microfilaria malayi. (*From " A Comparative Study of Anatomy of Microfilaria Malayi and Bancrofti"* (Feng).)

The transmission through the mosquito intermediary has been worked out in the Dutch East Indies, India, Malaya, Ceylon, and China. The main genus is *Mansonioides* (p. 994), of which all species are crepuscular or nocturnal feeders. Development is more rapid than in *Wuchereria bancrofti* and lasts six and a half to eight and a half days. In Celebes, according to Brug and Tesch, development takes place in *Anopheles barbirostris* (99 per cent.). Gaillard has shown that in Indo-China it will not develop in *Culex fatigans*. In China *Anopheles hyrcanus*, var. *sinensis*, is effective. Of Mansonioides, *M. annulatus, M. annulifera, M. longipalpis*, and *M. uniformis* are equally suitable, and all are widely distributed wherever the water plants they favour are abundant. The larvæ of the insects adhere to the roots of *Pistia stratiotes* (water lettuce) by a specially constructed respiratory syphon which abstracts oxygen from the roots of the plant; this has been amply demonstrated by fine studies of Iyengar in Travancore. (Fig. 318, p. 994.)

Apparently filariasis associated with microfilaria malayi has distinctive features and may produce elephantiasis of the legs (p. 775). Eradication of water plants is the only practical measure in the control of this infection.

Iyengar has shown that both *W. bancrofti* and *Filaria malayi* are present in South India. The chief transmitter in the district of the latter is *Mansonioides annulifera*. The incidence of *W. bancrofti* is urban, while that of *Filaria malayi* is rural and depends upon the presence of ponds with water containing a high percentage of decaying matter and a growth of *Pistia stratiotes*. In the towns *W. bancrofti* endemicity shows a centripetal increase as against a centrifugal increase in the case of *Filaria malayi*. Iyengar has found that the species of mosquito infected with *W. bancrofti* in nature in these localities were *Culex fatigans*, *Mansonioides annulifera* (Fig. 319, p. 995), *Anopheles vagus*, *Anopheles subpictus*, and *Anopheles barbirostris*.

MANSONELLA OZZARDI (Manson, 1897; Faust, 1930)

Synonym.—*Filaria ozzardi* (Manson, 1897).

Manson first discovered the embryos of this species in the blood of aboriginal Carib Indians sent by Ozzard from British Guiana. In shape and size the embryos closely resembled those of *Acanthocheilonema perstans*; they were sheathless, but they had sharp tails, in contradistinction to the blunted extremity of that species. They observed no periodicity, and were present in the blood-stream both by day and by night. It was at first thought that similar embryos from natives of St. Vincent (Newsam) represented a different species, distinguished by Manson as *M. demarquayi*, but it is now generally recognized that only one species exists. *M. ozzardi* has been recorded from the West Indies and South America, while Manson found a similar microfilaria in the blood of an aboriginal of New Guinea, and this has been confirmed by Seligman. Some 25–30 per cent. of the inhabitants of the Northern Provinces of the Argentine Republic are infected with a similar species (Biglieri and Araoz). In British Guiana the microfilaria of *M. ozzardi* is nearly always found in the blood in conjunction with a microfilaria resembling that of *A. perstans*, an observation which has led to the suggestion that the species may be dimorphic.[1]

The parental forms of this microfilaria were first found by Daniels at the autopsy of two Demerara Indians; later, Galgey found five adult females

[1] Owing to this dimorphism and the close resemblance to microfilaria perstans, it is not possible at present to map out the exact distribution of these two species (*see* Map VI).

in the omental tissues of a native of St. Lucia. In Daniels's cases they were situated in the mesentery and the visceral fat. He stated that a male which he examined measured about 32 mm. in length; the tail was much coiled, and carried at least one spicule. The female is about 65–81 mm. long and 0·210 to 0·25 mm. broad. The head is somewhat club-shaped and bears no papillæ. The vulva is situated 0·76 mm. from the anterior extremity, the anus 0·23 mm. from the tip of the tail. The embryos measure 173–240 μ in length by 4–5 μ in diameter. As far as is known, this filaria is not pathogenic. The microfilaria is non-periodic. (*See* Fig. 128, *6*, p. 744.)

The life-history of this filaria has been worked out by J. J. C. Buckley (1934) in St. Vincent, B.W.I. The intermediary host is a midge, *Culicoides furens*, Poey, which is a common insect in Calliaqua, where 37·7 per cent. of the inhabitants are infected. Of the flies fed on infected blood, 27·5 per cent. were found to contain the developing stages of the parasite. As in the case of *W. bancrofti*, the ingested microfilariæ migrate within twenty-four hours to the thorax, where the entire larval development takes place. In those flies which were kept alive for seven or eight days, advanced stages were found in the thorax and head, and their emergence from the proboscis was observed.

The development of this filaria takes place on the same lines as that of *A. perstans*, from the first stage or "sausage" larva to the second stage larva during the first three or four days, and from this stage to a third stage, or infective larva, on the fifth or sixth day. Two ecdyses occur during these metamorphoses. The largest third stage larva in the head of the insect measures 0·78 mm. in length. It is possible that *Culicoides paræensis*, another species in Calliaqua, may also act, and in Antigua Island O'Connor found that *C. furens* is the vector.

Loa loa (Guyot, 1778)

L. loa (Fig. 151, p. 778) occurs throughout tropical West Africa. It is a parasite of man, as far as is known. A closely allied parasite has been described by Treadgold in *Papio cynocephalus* and named *L. papionis*.

The adult *male* measures 30–34 mm. in length, and presents a maximum breadth of 0·350–0·430 mm. in the anterior part of the body. (Fig. 270). The posterior part tapers gradually towards the tail. The measurements of the adult *female* have not been satisfactorily determined; the specimens so far examined, extracted from under the skin or from about the eyes of patients, varied greatly in length from 20 to 70 mm. The breadth is about 0·5 mm. (Fig. 271.)

L. loa is especially characterized among the nematodes of man by the presence of numerous rounded, smooth, translucent protuberances of the cuticle, 12–16 μ in diameter, and rising 9–11 μ above the general surface. These chitinous bosses vary greatly in number and arrangement in different specimens, and are, as a rule, more numerous in the female. Their distribution is very irregular. In the male they are wanting at the extremities, beginning about 1·5–2·5 mm. from the mouth and tail-tip respectively. In the female they usually extend to the posterior extremity, and may also be found on the cephalic end.

The body is filiform, cylindrical, whitish, semitransparent. Anteriorly it tapers somewhat abruptly to the mouth, which is terminal, small, simple, unarmed, and apparently destitute of papillæ. There is no distinctly marked neck, but there is a sort of shoulder about 0·15 mm. from the mouth, and

at about this level are two small papillæ, one corresponding to the dorsal, the other to the ventral median line.

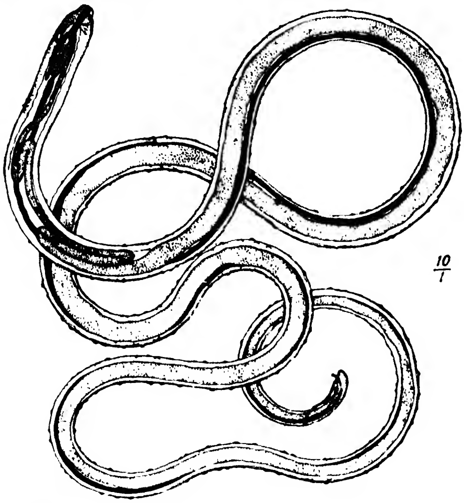


Fig. 270.—*L. loa*, male. × 10. (*Partly after Looss.*)

The alimentary tube begins at the oral cavity, which is funnel-shaped and surrounded by a strong muscular mass. It consists of a slender œsophagus

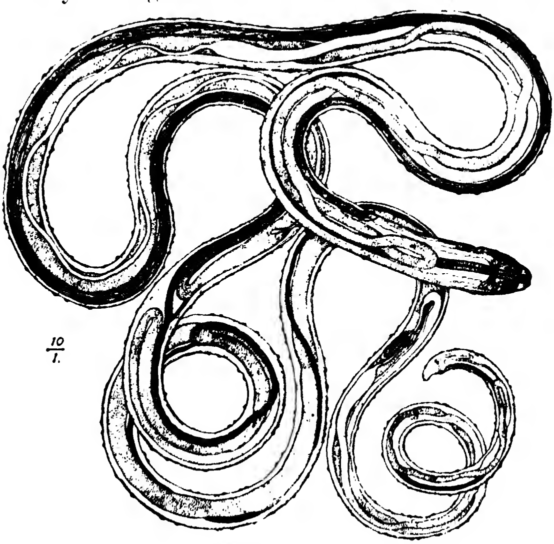


Fig. 271.—*L. loa*, female. × 10. (*Partly after Looss.*)

without bulb, of an intestine attaining a width of about 65 μ towards the middle of the body, and of a short, attenuated rectum.

The tail of the *male* is slightly curved ventrally and provided with two lateral expansions of the cuticle (0·7 mm. long by 0·029 mm. broad), situated nearer the ventral than the dorsal surface. In the middle of the ventral surface, between the lateral alæ, and about 0·08 mm. from the tail-tip, is the opening of the ano-genital orifice, from which two unequal spicules may be seen protruding; the longer measures 123–176 μ, the shorter 88–113 μ; the opening is surrounded by thick labia. On either side, and somewhat asymmetrically placed, are four large globular and pedunculated papillæ closely approximated and decreasing in size antero-posteriorly. Farther back, and nearer to the middle line, is a fifth symmetrical pair of very small, conical, postanal papillæ with broad base and acuminated point. (Fig. 272, B.)

The posterior extremity of the *female* is straight, attenuated, and broadly rounded off. The vulva forms a small eminence about 2·5 mm. from the anterior extremity. The vagina, 9 mm. long and 95 mm. wide, branches off into two long tubes extending almost throughout the entire length of the body. (Fig. 272, A.) These tubes, the narrow ends of which are the ovaria, contain eggs in all stages of development. The mode of reproduction is ovoviviparous, the embryos developing within the egg envelope and uncoiling

Fig. 272.—Posterior extremity of *L. loa*, (A) female, (B) male. (*After Looss.*)

themselves on expulsion from the vagina in a similar manner to that of microfilaria bancrofti.

The embryo.—Microfilaria loa (or, as it is sometimes called, microfilaria diurna) is very similar in size (298 μ by 7·5 μ) and structure to that of microfilaria bancrofti. Although in the fresh liquid blood it is practically impossible to distinguish, with the microscope alone, the living microfilariæ of the two species, in dried and stained films certain more or less pronounced differences can be made out. (1) In such preparations microfilaria bancrofti is usually disposed in sweeping curves; microfilaria loa, on the other hand, assumes a stiff, ungraceful, almost angular attitude. (2) The tail end of microfilaria loa is often disposed in a series of sharp flexures, giving it in some instances a corkscrew-like appearance, the extreme tip being always sharply flexed. (3) The nuclei of the central column of cells of microfilaria loa are larger and stain less deeply than those of microfilaria bancrofti, and, as a rule, the cephalic end of the column is more abruptly terminated in the former. Although in most slides one or two specimens may be hard to diagnose, on the average of a series of preparations the foregoing distinctions are recognizable. Fülleborn, by special staining methods, points out various other minor differences among which the *large genital cell* is a marked feature.

The presence of red-staining substance "Innenkörper" is characteristic of microfilaria bancrofti; but not of microfilaria loa; the latter is never found in hydrocele fluid, while the former commonly is. (Fig. 128, *2*, p. 744.)

Sharp (1923) has pointed out that certain differential characteristics may be distinguished in the living embryos by staining with methylene-blue. A drop of blood is placed upon a drop of this stain, 1 : 5000; if the embryo is that of *L. loa* it begins to take up the stain in ten minutes, while in the case of microfilaria bancrofti absorption is much slower and the stain picks out the excretory pore.

In some instances the embryo may not appear in the peripheral blood-stream of a patient infected with *L. loa* till a period of six, or even seven, years has elapsed.

Life-history.—Development proceeds, in much the same manner as in the case of *W. bancrofti*, in the body of certain day-biting, blood-sucking flies, "mangrove flies," *Chrysops silacea* and *C. dimidiata*. (Fig. 328.) On entering the stomach of these insects the embryo casts its sheath within three hours and, piercing the stomach-wall, enters the thoracic muscles, the connective tissue and fat-body (Stevenson) of the thorax and head, but principally that of the abdomen. Larval development is complete in ten days. In three days the developing filaria has broadened out and has assumed a torpedo-shape; shortly afterwards the intestinal canal becomes formed. On the fourth and fifth days the short, squat form becomes lengthened out to 0·8 or 1 mm.; on the sixth the corkscrew appearance is replaced by gentle curves, and the first ecdysis takes place; the sharp-pointed tail is then replaced by a gently-rounded and trilobed extremity. The larva continues to grow so that by the tenth day it measures 2 mm. in length by 0·025 mm. in breadth. (Fig. 273.) The larvæ have now congregated in the head in large numbers, the majority being found at the root of the proboscis, and make their way out to the surface of the skin of the intermediary host, breaking through the proboscis sheath when the infected fly feeds. (Fig. 274.) The flies themselves can remain infective for five or six days. The Connals have found that in Calabar 3·5 per cent. of the wild-caught flies are naturally infected with *Loa loa*.

For Pathogenesis, *see* pp. 779-782.

ACANTHOCHEILONEMA PERSTANS (Manson, 1891; Railliet, Henry and Langeron, 1912)

Synonym.—*Dipetalonema perstans.*

The adult worm was discovered by Daniels in Demerara Indians, and subsequently identified by Manson. The embryo, or microfilaria, was first discovered in the blood by Manson in 1891.

The embryo of this parasite is very common in the blood of the natives of large districts in tropical Africa, and apparently occurs also in the chimpanzee. It has been recorded from the Congo, Nigeria, the Gold and Ivory Coasts, and in Sierra Leone. It is common in Northern Rhodesia and in Uganda, where in some districts it may be found in 90 per cent. of the population. A microfilaria resembling it is reported from Western Venezuela, Trinidad, British and Dutch Guiana, the valley of the Amazon, and Northern Argentina. It probably also occurs in New Guinea.

It is frequently encountered in the blood of Europeans who have resided in Central Africa. Sometimes it occurs along with microfilaria loa and

microfilaria bancrofti, and in British Guiana with microfilaria ozzardi, in the same individual.

The South American form may very well be a distinct species, as the microfilariæ are morphologically similar and the adult parasites are insufficiently known. (Map VI, facing p. 745.)

A. perstans is, like *W. bancrofti*, a long, cylindrical, filiform nematode. The body is smooth, without markings; the mouth simple and unarmed. The tail in both sexes is peculiar and characteristic; it is incurvated, and the chitinous covering at the extreme tip is split up, as it were, into two minute triangular appendages, giving it a mitred appearance. The *male* is smaller than

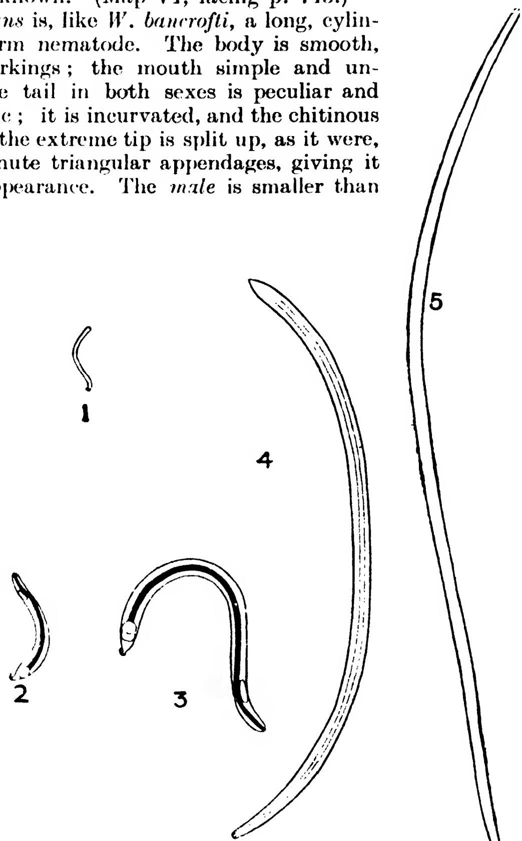


Fig. 273.—Development of *Loa loa* in chrysops. × 30.
(*After A. and S.L.M. Connal. "Trans. Roy. Soc. Trop. Med."*)
1, Larva, 24 hours old; 2, fourth day (length 390 μ); 3, fifth day; 4, seventh day (length 1·5 mm.); 5 tenth day (length 2 mm., breadth 0·025 mm.).

the female; it measures 45 mm. in length by 0·06 mm. in breadth. The diameter of the head is 0·04 mm. Close to the opening of the cloaca there are four pairs of preanal and one pair of postanal papillæ. Two unequal spicules may be seen protruding from the cloaca. (Fig. 275.) The adult *female* measures 70 to 80 mm. in length by 0·12 mm. in breadth. The head is club-shaped and measures 0·07 mm. in diameter. The genital

pore opens at 1·2 mm. (Chesterman) from the head. The anus opens at the apex of a papilla situated in the concavity of the curve formed by the tail. The diameter of the tail just before termination is 0·02 mm.

The adult worms are sometimes found in numbers in the mesentery and in the perirenal and retroperitoneal tissues, and in the pericardium. According to Brumpt, they generally occur singly, and cause no reaction of the surrounding tissues.

Fig. 274.—Development of *L. loa* **in** *Chrysops silacea*, **showing several mature larvæ at tip of labella.**
(*After A. and S. L. M. Connal, "Trans. Roy. Soc. Trop. Med. and Hyg."*)

The embryo. — Microfilaria perstans observes no periodicity, being present in the blood both by day and by night, but its numbers at different times may vary considerably. In this respect it resembles microfilaria ozzardi. Its special seat of selection is not the peripheral blood, but that of the heart, lungs, aorta, and other large vessels. It has not been found in the spleen and only rarely in the liver and pancreas. The embryo in the blood measures on an average 200 μ by 4·5 μ; but, as it possesses in a remarkable degree the power to elongate and to shorten itself, these measurements do not always apply. (*See* Fig. 128, *5*, p. 744.) Brumpt and others recognize a long and a short form, the latter being 90–110 μ in length by 4 μ in breadth. It is manifestly much smaller than the microfilaria of *W. bancrofti* or of *Loa loa*, and is further distinguished from them by the entire absence of a sheath and by the characters of its caudal end, which is invariably truncated and abruptly rounded off. The taper which terminates in the tail extends through quite two-thirds of the entire length of the embryo. The V-spot is about 0·03 mm. from the cephalic extremity. There is no marked tail-spot. No hooked cephalic prepuce can be made out, and according to Fülleborn, no red staining "granular mass" (*Innenkörper*), can be demonstrated. Its movements also differ from those of

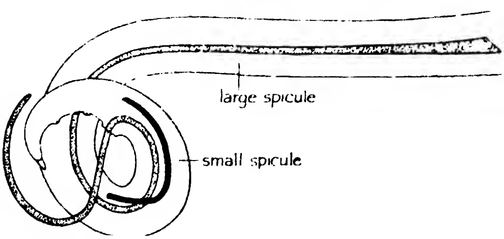


Fig. 275.—Tail of *Acanthocheilonema perstans*, **showing two unequal spicules and papillæ.** (*After Leiper.*)

microfilaria bancrofti, for it not only wriggles about, just as that parasite does, but indulges in long excursions through the blood, moving freely all over the slide—locomoting, in fact, very much in the same way as the other species do in the insect's stomach after they have cast their sheaths.

Dyce Sharp has worked out the cycle of development of *A. perstans* in small midges—*Culicoides austeni* and *C. grahami*, in the Cameroons. The embryos when ingested undergo development in the wing muscles in the same manner as *W. bancrofti*. Within six to nine days the larval filariæ are ripe for emergence in the proboscis where they generally appear in pairs. Previous to emergence there occurs a globular expansion of the labrum which eventually collapses and gives exit to the filariæ (Sharp). (Fig. 276.) They measure at that time 0·7 mm. in length. About 7 per cent. of wild midges are naturally infected. Considerable difficulty is experienced in keeping these small insects alive in confinement, unless they receive a second feed of blood.

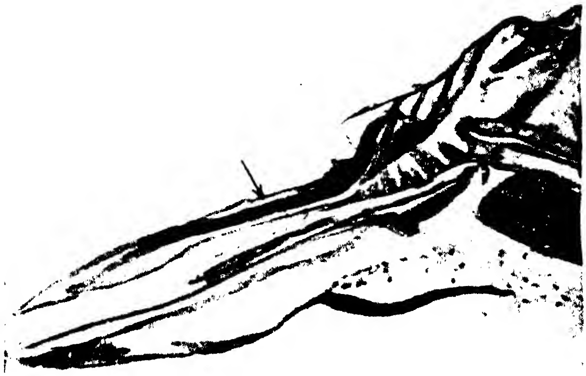


Fig. 276. - Larva of *Acanthocheilonema perstans* in proboscis of *Culicoides austeni*. (*Dyce Sharp. Microphoto: Dr. A. C. Stevenson.*)

A. perstans appears to be particularly harmless to its host. It is surprising that in its wanderings in the mesentery it does not give rise to greater disturbance; possibly transient abdominal pains in the region of the gall-bladder may be attributed to its presence. As already related it may form, occasionally, subcutaneous cysts. Probably, too, according to the Editor's observations, like *L. loa*, it gives rise to painless, Calabar-like swellings—a phenomenon which is now regarded as an allergic manifestation.

Onchocerca volvulus (Leuckart, 1893; Railliet and Henry, 1910)

This parasite inhabits the subcutaneous tissues of man, especially the intercostal spaces, the axilla and popliteal space, and suboccipital region. It is found in tropical Africa, especially the West Coast, and Guatemala.

The body is white, filiform, and tapering at both ends. The head is rounded, with a diameter of 0·04 mm., and the cuticle is marked by transverse ridges. The cuticle is raised with prominent angular and oblique thickenings, which are more distinct posteriorly.

The *male* is 20–40 mm. in length by 0·2 mm. in breadth. The alimentary canal is straight, and ends in a subterminal anus. The tail terminates in a single spiral, and is bulbous at the tip. There are two pairs of preanal, two pairs of postanal, and an intermediate large papilla. Two unequal spicules, measuring 0·082 and 0·177 mm. respectively, may be seen protruding from the cloaca. (Fig. 277.)

The *female* is of very considerable length, measuring 60–70 cm by 0·4 mm., but more recent measurements are considerably smaller, giving a length of 35–40 cm. (Schäfer).

The head is rounded and truncated, and measures 0·04 mm. in diameter. The vulva is situated 0·85 mm. from the anterior extremity, and the tail is curved. The cuticular striations are said to be not so distinct as in the male. *O. volvulus* is ovoviviparous. The egg possesses a peculiar striated shell, and has a pointed process at each pole (like an orange wrapped in tissue paper), and measures 30–50 μ in diameter. At least four males and two females are present in every tumour.

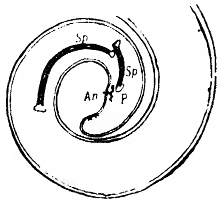


Fig. 277.—Caudal extremity of *Onchocerca volvulus*, ♂. (*After Brumpt.*)

Sp., Spicules; *An.*, Anus; *P.*, papillæ.

The *embryo* is sheathless, and measures 300 μ in length by 8 μ in breadth as a general rule; though in the fluid of the cyst-cavity in the surrounding skin, two types, a larger and a smaller one, are present (Blacklock). The body tapers from about the last fifth of its length, and ends in a sharply-pointed recurved tail. (Fig. 128 4, p. 744.)

At about the anterior fifth of the body there is a gap in the central column of cell (V-spot). There is a slight thickening behind the cephalic cone at the commencement of the nuclear column. The embryo is non-periodic in habit, and has been found rarely in the blood (Fülleborn), in the femoral, inguinal, and cervical lymph-glands, and in the expressed juice of tumours.

According to Macfie and Corson, these embryos are found in the normal skin of widely separated portions of the body of apparently healthy natives (34 per cent.) of the Gold Coast. Dyce Sharp and others have shown that *O. volvulus* may be the cause of massive elephantiasis of the legs (*see* p. 784).

Blacklock, working in Sierra Leone, where in certain parts 45 per cent. of the inhabitants harbour embryos of *O. volvulus* in their skins, often unassociated with any pathological condition, has traced the development of this filaria in the "buffalo-gnat"—*Simulium damnosum.* (Fig. 323.) The fly abstracts the embryo from the deeper layers of the skin near the nodule. The embryos enter the stomach and, piercing its walls, come to lie amongst the thoracic muscles where they undergo a development similarto that of *W. bancrofti* in the mosquito. During their growth one or more ecdyses probably take place (Blacklock). After seven days the larval filaria measures 657 μ. Development has been traced up to the tenth day and, probably, the larva escapes from the proboscis as in the case of other filariæ. *S. damnosum* bites from 6 a.m. to 6 p.m. Dissection of wild-caught simulium flies showed that 2·6 per cent. were naturally infected. Dyce Sharp has shown that this insect has a selective action in abstracting the embryos of *O. volvulus* from the blood. By scraping the skin with its prestomal teeth it sucks up the serum from the wound and with it the filarial embryos.

Brumpt has separated the South American form of *O. volvulus* under the name of *O. cæcutiens* (Brumpt, 1919), but this is doubtfully a valid species. It is said to differ from *volvulus* in the size and shape of the papillæ in the male, in the size of the spicules, and in its association with eye and skin lesions (*see* p. 784). The eye symptoms—keratitis punctata and interstitial keratitis—may lead to blindness in some cases.

Strong describes the development of the South American form as similar to that of the Central African. It takes place in *Simulium avidum*, *S. ochraceum*, and *S. mooseri*, species which abound in the endemic areas of onchocerciasis in Guatemala. When these insects have gorged themselves upon a suitably infected individual, the microfilariæ, which are not digested or killed, pass from the gut to other parts of the fly, particularly to other parts of the abdomen and to the thoracic muscles. At first 200–300 μ in length, they soon become broader—from 22–25 μ in breadth—and the caudal appendage becomes transformed into a short-pointed tail. Two caudal papillæ can usually be distinguished. Two ecdyses apparently take place. The developing parasites commonly inhabit the Malpighian tubes. The most fully developed forms in *Simulium* measure from 450–1,140 μ in length and usually from 16 to 25 μ in breadth. The fourth, or infective, larval stage is found in the head of the insect after a period of ten days, or longer.

In dissection of 2,088 simulium flies caught in Guatemala in 1931, Strong has found 11 per cent. to contain some stage of *Onchocerca cæcutiens*.

For pathogenesis and eye symptoms, *see* pp. 783–787.

MICROFILARIA STREPTOCERCA (Macfie and Corson, 1922; Stiles and Hassall, 1926).

Under the name of *Agamofilaria streptocerca*, Macfie has described a sheathless microfilaria as being commonly found in the corium of the skin, but not in the blood-stream, of natives of the Gold Coast, for he found it in 22 out of 50 men examined at Accra. The adult nematodes are as yet unknown. The embryo measures 215 μ in length, and can be distinguished, according

Fig. 278.—*Agamofilaria streptocerca* embryo, showing characteristic curvature of tail. × 200. (*Dyce Sharp.*)

to Dyce Sharp, by the "walking-stick handle" appearance of the tail extremity. Recent experiences have shown that this filaria has a wide distribution and is common in the Cameroons. The arrangement of the nuclei in the head and four rounded ones in the tail are distinctive and afford an index of differentiation from the embryo of *O. volvulus* and *A. perstans*. The insect vector is at present unknown. (Fig. 278.)

DRACUNCULUS MEDINENSIS (Linn., 1758)[1]

GUINEA-WORM

This worm lives in the subcutaneous tissue of man, especially of the leg, arm, and back. Its occurrence in the ox, horse, dog, wild-cat, jackal, and leopard is now regarded as accidental, though dogs, monkeys and cats can be experimentally infected.

[1] According to Leiper, Dracunculus is not a valid generic name for the guinea-worm; he has proposed the name *Füllebornius* to replace *Dracunculus*, but the latter name has been definitely sanctioned by the International Commission of 1915.

D. medinensis is a common parasite of man in India and Africa apparently, and has been imported into the West Indies and South America. In Guiana and Brazil it has now become endemic.

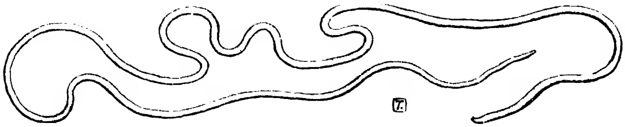


Fig. 279.—*Dracunculus medinensis.* One-third nat. size.

The *female* is reputed to attain, in some instances, enormous dimensions; it is probable, however, that worms of 5 ft. or 6 ft. in length owe their size to errors of observation—two worms, or their fragments, having been regarded as one. According to Ewart, in forty carefully measured specimens the smallest was about 32·5 cm., the largest 1 m. 20 cm. in length; 90 cm. is probably an average length. The diameter of the worm is about 1·5–1·7 mm. The body is cylindrical, milky-white, smooth, and without markings (Fig. 279). The tip of the tail comes to a point and is abruptly bent, thus forming a sort of blunted hook. The head end is rounded off, terminating in what is known as the cephalic shield. The mouth is triangular, very small, and surrounded by eight papillæ. (Fig. 280.) The alimentary canal is relatively small, being compressed and thrust to one side by the branched uterus; in the mature worm it is probably cæcal, for it has not been traced to an anus. Nearly the whole of the worm is occupied by the uterus, which is packed with coiled up embryos. (Fig. 281.) Each branch of the uterus ends in a short ovary. The vagina also may be lacking or extremely difficult to detect. Leiper has shown that the worm discharges its young by a prolapse of the uterus, as described by Manson, and that the extrusion does not occur through

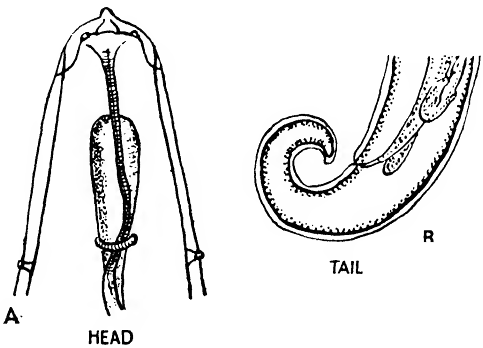


Fig. 280.—Anterior end and tail of *D. medinensis.* × 10. (*After Faust.*)

the mouth, as suggested by Looss and Manson, but by a rupture just outside the circumoral ring of papillæ, possibly through the uterus itself.

According to Polak, the Persians have long known the *male* to be a smaller worm, 7–10 cm. long. They also stated that at times as many as twenty of these small worms might be found coiled round a female specimen. A shorter

(4 cm.) worm is described and has been regarded as the male, attached to the larger female worm within the subperitoneal connective tissue. Daniels, at the post-mortem of a monkey experimentally infected by Leiper six months previously, found three immature females (30 cm. long), and two remarkably small males (2·2 cm.) which were obtained, one from the psoas muscle, and the other from the connective tissue behind the œsophagus.

Moorthy (1937) has once again found the male form in an experimental dog killed 103 days after infection. Nine males and 23 females were present, the former measuring 2·1–2·9 cm. in length; one was actually present in the meninges. The males have equal spicules 490–730 μ in length and a gubernaculum 200 μ in length. The finding of living *male* forms in the tissues of experimental dogs affords evidence that copulation takes place in the deeper body tissues, and not, as some have considered possible, in the intestinal

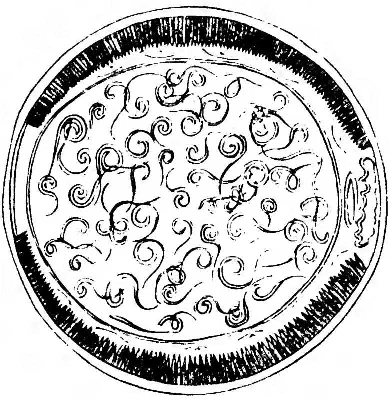


Fig. 281.—Transverse section of *D. medinensis, showing contained embryo.* (*After Leuckart.*)

tract. The later history of the male is still obscure, possibly, when it has performed its function, the creature is absorbed.

The *embryos* (Figs. 281, 282) measure 650–750 μ long by 17 μ broad. According to Looss, they are flattened, not cylindrical. They are provided with a long, slender tail, a rounded head, an easily distinguishable alimentary canal, a rudimentary anus, and a bulbous œsophagus. The cuticle is transversely striated. Two peculiar glandular organs are situated in the root of the tail.

The embryos, in swimming, move by a sort of side-to-side lashing of the tail and tadpole-like motion of the body. The movements are intermittent, sudden short swims alternating with brief pauses. When progressing, the greater transverse axis of the body is perpendicular to the plane travelled over.

Moorthy has described *abnormal* embryos exhibiting prominences on the dorsal and ventral caudal surfaces; but they do not survive.

In clean water the embryo remains alive for six days; in muddy water or in moist earth it will live from two to three weeks. If slowly desiccated

it does not die, but may be resuscitated by being again placed in a little water.

Transmission.—Historically, Fedchenko is credited with the discovery of the life-cycle of the guinea-worm in cyclops. Leiper asserts that it was by observing the development of *Cucullanus* in cyclops which led Leuckart to suggest to Fedchenko that *Dracunculus* did the same. Apparently, the figures published by the latter as those of *Dracunculus*, were really those of *Cucullanus*. To Manson, then, must be given the credit for his original observations on this matter (1895).

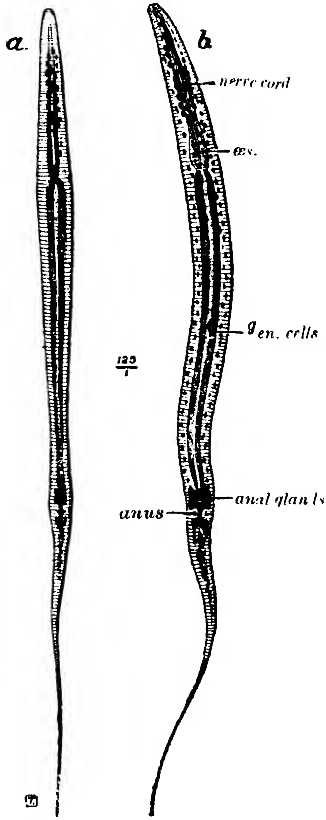


Fig. 282.—Embryo of *D. medinensis* × 150.
a, Side view ; *b* (*after Looss*), front view.

If dracunculus embryos are placed together with *Cyclops quadricornis*, or allied species (*C. strenuus*, *C. viridis*, *C. coronatus*, *C. bicuspidatus*, *Mesocyclops leuckarti*, and *M. hyalinus*), in a watch-glass, after a few hours the embryos will have been ingested by the cyclops (Fig. 283), where they can be seen moving about, coiling and uncoiling themselves, with considerable activity. Apparently the jerky movements of the embryo attract the cyclops in the same way as a trout is attracted by a

fly, and the crustaceans actually do hunt this embryo. As many as fifteen or twenty larvæ may be counted in each crustacean, which, unless the infection is excessive, seems in no way inconvenienced. After a time the embryos so transferred undergo a metamorphosis. They cast their skins two or three times, get rid of their long, swimming tails, acquire a cylindrical shape, and ultimately, along with increased size, develop a tripartite arrangement of the extreme posterior end, as in *W. bancrofti* and *Loa loa*. The rate of development varies according to the temperature; usually it takes four to six weeks. This larva is 1 mm. in length, and at this stage it is ingested by man and completes its development in the connective tissues. Development of the adult worm is believed to take about a year.

According to Liston, 38·6 per cent. of the cyclops in some Indian villages are infected; while Chatton in Dahomey records a much higher figure. The latter has suggested that the same species of cyclops does not necessarily form the most suitable intermediary host in the various countries in which the guinea-worm is endemic. In Tunisia the appropriate species appears to be *C. viridis*.

Larvæ protruding from thorax

Fig. 283.—Embryos of *D. medinensis* in body-cavity of cyclops.

(*Manson's original preparation. Photo: Mr. Andrew Pringle.*)

The cyclops has been slightly compressed so as to force out some of the worms, which can be seen escaping from ruptures at the head and tail.

(For further details *see* pp. 788–795.)

III. MEDICAL ENTOMOLOGY

ARACHNIDA (MITES AND TICKS)

(A) MITES

SARCOPTES SCABIEI (Linn., 1758)

ITCH-MITE (Figs. 284, 285)

Morphologically identical species are found on all domesticated animals, as well as on foxes, wolves, and the llama. They can maintain a temporary existence on the human skin.

The female is 0·3–0·4 mm. in length, the male 0·2 mm. The latter is provided with a penis situated at the fourth pair of legs. The sexes may be distinguished by the epimera of the second pair of hind-legs, which unite with the sexual orifice in the male, but in the female are free: the hind-leg in the male is provided with a sucker; in the female, with a bristle. The gravid female lives in a burrow in the skin, at the entrance of which the male keeps watch. The eggs, measuring 150 μ in length by 100 μ in breadth, are laid in the burrow, 40–50 in number, and give rise in a period of three to five days to larvæ, which pass through four stages in a period of about three weeks. In the first stage the hexapod larva moults several times, becoming an octopod nymph, characterized by 12 dorsal spines. The third stage is entered about the twentieth day, when the nymphs moult and become sexual males and females, which pair off. During the fourth stage the impregnated female moults once more and develops a sexual orifice; she then burrows into the skin and deposits the eggs. The average life of the adult parasite is four to five weeks (Munro).

Prevention and treatment of scabies.—The promiscuous use of blankets and the lack of washing facilities aid in the spread of the disease. Preparatory to treatment the patient should be well washed in a hot bath (106° F.) containing 2 oz. of washing soda. He should be instructed to immerse himself in this for twenty minutes. The body is then scrubbed well with soft soap and a scrubbing brush, the hands with a stout tooth-brush. The burrows are thus torn open and the acari removed or exposed to the parasiticide. After drying, the patient is rubbed all over with a piece of lint dipped in 3 oz. of liquor calcis sulphuratus B.P. It is important that a fresh solution be used for each case; if the skin is very sensitive, it may be necessary to dilute the solution at first. If this solution cannot be obtained, unguentum sulphuris, 2 oz. at a time, should be thoroughly rubbed in for at least twenty minutes. The treatment of scabies by sulphur fumigation is useless.

Mitigal (Bayer & Co.), a hydrocarbon compound containing sulphur, is less irritating and possesses no unpleasant odour. It is rubbed into the affected area for three consecutive evenings and allowed to dry on. The patient should be forbidden to wash. *Kathiolan* is the Danish preparation and is very active; it is the one used in the British Navy.

Huber has described a new practical and quick method of treating scabies as practised in Germany and Hungary. The whole body, with the exception of the neck and face, is painted with a 40-per-cent. solution of sodium thiosulphate ("hypo"). After fifteen minutes for drying, the skin is rubbed with 5-per-cent. hydrochloric acid, this also being left to dry for fifteen minutes. The whole process is repeated, and the patient puts on clean linen. On the next day the application is repeated in exactly the same manner.

Kissmeyer (1937) recommends a rapid ambulant treatment with a benzyl benzoate lotion as follows:

Soft soap (B.P. 1932)
Isopropyl alcohol, $(CH_3)_2\,CH.OH$
Benzyl benzoate, $C_6H_5COOCH_2C_6H_5$

The quantity necessary for each patient is 350 grm.

The treatment is carried out in forty-five minutes without any damage to the skin, and is inexpensive. The whole body is anointed with soft soap, and the patient then soaks in a warm bath at 100° F. for ten minutes. While still wet, the body is brushed all over with the lotion, using a brush of Russian pigs' bristle. Twenty-four hours later, a second bath is taken.

Pediculoides, especially the species *P. ventricosus* (Fig. 109, p. 704), is parasitic on insects and is often found in raw cotton, which has given rise to epidemics of itch among stevedores unloading cotton ships. The abdomen of the pregnant female of this species becomes swollen with eggs, like a small chigger. In it the eggs hatch and the young complete their development, to issue forth as adults.

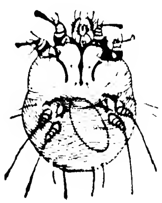


Fig. 284. — *Sarcoptes scabiei*: **ventral aspect.** × 35. (*After Canestrini.*)

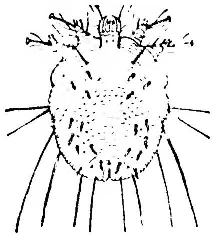


Fig. 285.—*Sarcoptes scabiei*: **dorsal view.** × 40. (*After Brumpt.*)

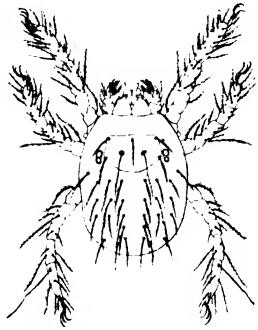


Fig. 286. — *Leptus autumnalis.* × 50. (*After Hirst, "Journ. Economic Biol."*)

TROMBIDIIDÆ

The family Trombidiidæ are large, bright-red creatures, known as velvet mites, predaceous on their own kind and other insects, while some are very destructive to plants. The larvæ of this family may infect the human skin, causing very severe itching, and are known as harvest-bugs. The orange-coloured larva, *Leptus autumnalis*, 0·5 mm. in length, is produced from eggs which are deposited by the parents on the ground (Fig. 286). The adult form is unknown. Normally this mite is parasitic on moles and hares; it only lives for a few days on man. The injection of toxins by these small creatures is effected by the stylostome—a long suctorial tube formed by the salivary secretions, by means of which the larva penetrates the skin of its host and digests the surrounding tissues. The wall of this tube is formed by solidified secretion from the mouth, and becomes detached and left in the tissues when the replete larva quits its hold. Inunction with oleum cajuputi, or bandaging the irritated part with material soaked in a weak solution of subacetate of lead or sulphate of copper, gives relief.

Other species of medical interest are *Trombicula akamushi*, *T. schüffneri* and *T. deliensis*, the Kedani mite, or intermediary hosts of the virus of

Japanese river fever. (Figs. 287, 288.) The form which transmits the disease is the hexapod larva of a mite (*Trombicula akamushi*), and lives on the field-vole (Microtus), the house-rat of Formosa (*R. rattus rufescens*), and other

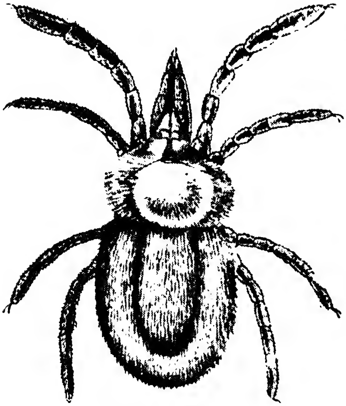


Fig. 287.—*Trombicula akamushi* : **full-grown imago.** × 35. (*After Mizajima and Okumura.*)

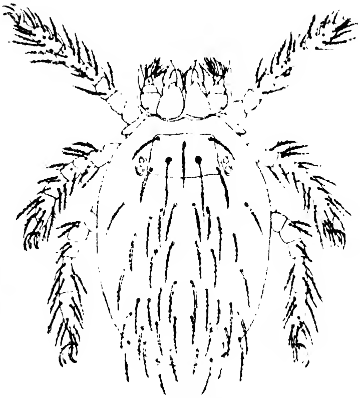


Fig. 288.—**Larva of** *Trombicula akamushi.* × 80. (*After Hirst, "Journ. Economic Biol."*)

rodents. The adult form, or *Trombicula*, is found in the soil of infected fields; it is a tiny creature 0·9 mm. in length by 0·5 mm. in breadth, is pale-grey or red in colour, with two rudimentary eyes and four pairs of legs; the anterior pair of legs are stout, and are carried on the anterior part of the cephalothorax parallel to the pedipalps. On the ventral surface are situated two pairs of suckers close to the genital orifice and the anus. The larva, or *leptotrombicula*, measures 0·4 mm. in length by 0·25 mm. in breadth and resembles *Leptus autumnalis* in general appearance, but the legs and pedipalps are stouter, and the body, including the legs, is covered with minute plumose hairs. The cephalothorax bears a pair of eyes conspicuously red in colour. The nymph has a peculiar figure-of-eight shape, an abdominal constriction dividing the body into two parts. It measures 0·65 mm. in length, and in due season moults and becomes adult. (*See* also, pp. 270, 271.)

Harvest-bugs occur in practically every part of the world and are especially annoying in some parts of the tropics. In Surinam there is a very virulent form known as *Acarus balatus*; in New Guinea and Celebes the *Microtrombidium wichmanni*, in South America the *Microtrombidium molestissimum*, or " Bicho Colorado," are the best known.

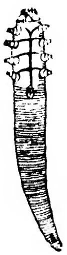


Fig. 289.—*Demodex folliculorum.* × 100. (*After Brumpt.*)

Demodex folliculorum var. hominis (Simon, 1842)

This parasite (Fig. 289) lives in the hair-follicles and sebaceous glands around the mouth and nose of man. Similar species are met with in most domestic animals, as in the case of *Sarcoptes*, and are very minute, 0·3–0·4 mm. in length. The abdomen is marked off from the cephalothorax, and is elongated and transversely striated. The anal opening is situated at the junction of the cephalothorax and abdomen. The head is provided with a prominent rostrum—there are no vestiges of eyes; the mouth is adapted for sucking, and is provided with various

rudimentary appendages. The cephalothorax has four pairs of very short and stumpy legs with terminal rudimentary claws. In order to demonstrate them, one should express the sebum from the mouths of the sebaceous glands or comedones, and examine under a microscope in a drop of oil or xylol. If the condenser is shut down, one can distinguish the different larval stages.

The female lays heart-shaped eggs, 60–80 μ long and 40–50 μ broad, which on hatching give rise to hexapod larvæ ; after moulting several times these become sexually mature. All stages of development are passed within the follicles, but the mature parasites are believed to migrate over the skin. As regards their pathogenic rôle, they are responsible for inflammation of the eyelids when they occur in the Meibomian glands.

(B) TICKS (IXODOIDEA)

The Ticks are cosmopolitan in their distribution, and are interesting as carriers of various diseases. With the exception of *Argas* and *Ornithodorus*, in the adult state they rarely voluntarily attack man. Ticks are always visible to the naked eye, and the females are invariably larger than the males ; in some species the fully engorged females may measure nearly half an inch in length. They are divided roughly into two classes—*soft* and *hard*.

Life-history.—After impregnation the female tick attaches herself to her host. Becoming enormously distended with its blood, she drops off and secretes herself in some convenient hiding-place where she deposits her eggs, which are small, yellowish grains, amounting in some cases to thousands. Oviposition begins from two to ten days after the host has been quitted, and goes on for several days. In due course (two or three weeks under favourable conditions) the eggs are hatched. The larvæ look like minute moving grains of sand ; they are characterized by having only three pairs of legs, no stigmata, and no sexual orifice. A suitable opportunity presenting, the larva attaches itself to a vertebrate host. After a period of growth, it goes through a first moult (ecdysis), and emerges from its larval skin as a *nympha*, provided with eight legs instead of six, and with a pair of large stigmata placed one on each side of the body, behind the fourth pair of legs. After a second period of growth and a second moult, it becomes sexually mature. In some species, as in the case of *Margaropus bovis*, the metamorphosis from larva to nymph, and from nymph to imago, takes place upon the same host, the parasite remaining attached during the process. In other species, as in the case of *Hæmaphysalis leachi*, the tick, before each moult, drops off as soon as it ceases feeding, and in consequence has to find a host three times during its life, instead of once. The life-history of the hard ticks—*Ornithodorus* and *Argas*—differs in many respects (*see* below). Having reached maturity, the sexes unite. After fertilization the male dies but the female proceeds to engorge herself with blood for the development of her ova.

On account of the difficulty of finding an appropriate host, ticks are at all stages endowed with a phenomenal capacity for fasting. Megnin found *Argas persicus* alive after a fast of four years' duration. The following is a short account of certain species of pathogenic importance :—

Soft Ticks (Argasidæ).

ORNITHODORUS MOUBATA (Murray, 1884). (*See* Plate VII, 3, facing p. 224)

This species is widely distributed in Africa, from Uganda and Somaliland in the east, and Congo and Angola in the west, to Namaqualand and the Transvaal in the south.

The body is rotund and oval in outline ; the colour, when the tick is alive, is greenish brown. The integument is hard, leathery, covered with close-set shining granules or tubercles, and marked both above and below

with symmetrically-arranged grooves. The females may attain about 8 mm. in length by 6 to 7 mm. in breadth ; they moult frequently.

In habit *Ornithodorus moubata* resembles the common bed-bug. It lives in the huts of the natives, hiding during the day in cracks in the walls and floors, or in the thatched roofs, and moving about actively during the night in search of nourishment. It attacks both man and beast. It feeds slowly, and would be unable to get much blood from any but a sleeping person. It deposits its eggs in batches of 50, 70, or 100. Dissection has shown that only a few eggs mature at a time. The fertility of the female is favoured by liberal feeding. She lays batches of eggs after each feed, but does not continue to moult. The eggs hatch in about twenty days. In this tick the larval stage is practically omitted. About seven days after oviposition the hexapod larva can be seen to be forming within the translucent egg-shell. About the thirteenth day the egg-shell splits, and about the same time the larval skin splits also, and the *eight-legged nymph* throws off simultaneously both the egg-shell and its larval skin. There are several nymphal stages. The largest nymphs may equal adults in size, and show a punctiform mark where the sexual orifice is situated in the adult.

An interesting feature, and one perhaps having a bearing on the ætiology of tick-transmitted diseases, pointing as it does to a channel by which the eggs may receive a germ ingested by the parent, concerns certain cells in the stomach-wall. The tick, while feeding, from time to time expels per anum a whitish material. This excretion is derived partly from the Malpighian tubes, and partly from the cells alluded to. In the stomach-wall, nourished by the imbibed blood, these cells elongate towards the cavity of the ventricle ; the other end, smaller and becoming clavate, splits and emits the elaborated nutriment into the general body-cavity, where it mixes with the blood of the tick. The cell then, becoming globular, drops into the lumen of the stomach, constituting part of the white excretion expelled per anum. One can readily understand how, by the former route, a parasite could reach the tissues of the tick, including the ovaries (*see* p. 217).

O. moubata is especially common along the routes of travel. The rest-houses are always the most infested. The ticks are frequently carried long distances in mats or bedding, or in porters' loads which have been piled for safety in the rest-huts at night.

The natives of some places, and also the Boers, protect themselves by plastering their huts, both floors and walls, with mud and cow-dung. The huts are also frequently smoked in order to drive the ticks from the thatch. A most valuable remedy for immediate use is the powder of the pyrethrum flower, which should be dusted between the sheets. Some protection may be obtained by keeping a lamp alight by the bedside at night.

In certain parts of Africa the distribution of *O. moubata* is overlapped by that of a closely allied species, *O. savignyi*, which is more diurnal in its habits and seems to have a predilection for market-places, cattle-stands, etc. *O. savignyi* is distinguished from *O. moubata* in being provided with eyes, in having larger processes on the legs and a more minutely pitted dorsal surface. *O. savignyi* has been recorded from Egypt, Nubia, Abyssinia, Somaliland, British East Africa, etc., as well as from Southern Asia. Its bite is dreaded.

ORNITHODORUS LAHORENSIS (Neumann, 1908)

In the nymphal state this tick lives on sheep in Central Asia. The adult lives in cracks and crevices in native houses and walls in Persia and Northern India, and emerges at night to bite man. This species has been suspected of carrying relapsing fever in Persia, but the evidence is not very conclusive.

ORNITHODORUS VENEZUELENSIS (Brumpt, 1921)

This tick is closely related to *O. talajé*, *O. capensis*, and *O. coniceps*. So far this species has been reported only from Venezuela and Colombia; it cannot live in the hot coastal plains where *O. talajé* abounds.

The female is larger than the male, measuring 5–6 mm. by 3–4 mm. broad. Its home is in the mountains, at an elevation of 3,000–5,000 ft., where it lives in the walls of human habitations, often in company with bed-bugs. In habits it is very voracious; it bites savagely and repeatedly whilst expelling a liquid coxal fluid. Its development has been studied by Brumpt.

The engorged, fecundated female lays 50–100 eggs, in several batches. The hexapod larvæ, on emerging, are very active, engorge themselves in a few hours on mammalian blood, moult, and give rise to a nymph which feeds without undergoing an ecdysis, as in *talajé* and *coniceps*. These evolutionary characteristics are the main points which led to its recognition as a separate species. The nymph moults after each feed, and becomes adult after the fourth. This tick conveys relapsing fever, probably hereditarily, as in *O. moubata*, in Colombia and Venezuela.

ORNITHODORUS ERRATICUS. (Lucas, 1849).

Synonym.—*O. marocanus* (Velu, 1919).

This tick inhabits piggeries, especially in Morocco. This appears to be an acquired habit, because under natural conditions it lives in burrows of various animals far from human habitations. The bites of this species are extremely painful. In Senegal, especially in Dakar, it transmits *Spirochæta duttoni* (syn. *Sp. crociduræ*) to man. In Spain and Morocco it transmits *Sp. hispanica*, especially in the hexapod larval state. The male is 3–4 mm. in length by 2–2·5 mm. in breadth; the female is 4–6·5 mm. in length by 2·5 to 4 mm. in breadth.

O. normandi (Larousse) is a very small Tunisian sub-species, reported to be a vector of relapsing fever.

ORNITHODORUS HERMSI (Wheeler, Herms and Meyer, 1935)

This small species lives in burrows of many rodents at an elevation of 4,000–7,000 ft., at Big Bear Lake, San Bernardino County, California, and can easily be distinguished from the other species, especially *O. talajé* and *O. turicata*. It transmits the Californian spirochæte, *Sp. turicatæ*. The female is of a sandy colour when not engorged, and is ovoid in shape, 5 mm. in length by 3·1 mm. in breadth. The male is similar in appearance to the female, and measures 3·8 mm. by 2·4 mm. This species differs from *O. talajé* in minor details, but especially in the smaller size of the male.

ORNITHODORUS PAPILLIPES (Birula, 1895)

Synonym.—*O. tholozani* (Laboulbène and Megnin, 1882)

This species, which rather resembles *O. talajé*, is widely spread in Palestine, Iran, and India, and is speeially abundant in Turkestan. It is known as the "Persian bug." It has now been found to transmit *Sp. persica* in the centres where it abounds. The male is 4-6 mm. in length, and the female may attain 8–9 mm. In nature it lives in the burrows of porcupines and jerboas. The evolution is the same as in *O. erraticus*.

ORNITHODORUS TALAJÉ (Guerin-Menéville, 1849)

This tick, measuring 5–6 mm. in length by 3–4 mm. in breadth, closely resembles *O. venezuelensis* and ranges from Mexico to Paraguay, but has recently been recorded also from the Gold Coast. It is nocturnal in its habits.

ARGAS PERSICUS (Fischer, 1824); A. MINIATUS (Koch, 1844) (Plate VII, 4, facing p. 224.)

This tick is found more commonly in the north and east of Persia, also in Syria, Turkestan, Russia, China, Algeria, and Cape Province, in North and South America and the West Indies, Western Australia and Queensland. It attacks both poultry and human beings, and infests old houses, living in the cracks of walls and floors.

Balfour has infected chickens with *S. gallinarum* by feeding them on the eggs of infected *Argas persicus*. This tick was formerly thought, on epidemiological grounds, to carry relapsing fever to man in Iran.

Hard Ticks (Iodidæ)

RHIPICEPHALUS SANGUINEUS (Latreille, 1804)

This tick, which is brown in colour, is a cosmopolitan species. In the tropics it is found all the year round, and lives on the dog, the whole cycle being completed inside the dog kennel. This tick usually uses three hosts, that is to say the larvæ, nymphs, and adults abandon the animal on which they are living after each repast. The female engorges herself with blood,

and immediately, on separating from the dog, lays 1,000–3,000 brown eggs, which hatch at 25° C.; after hatching, the larvæ attach themselves to a new host. At 15–20° C. the larvæ can live three to four months. This species can transmit the virus of typhus fever in South America and in South Africa, and also the fièvre boutonneuse of Marseilles.

HÆMAPHYSALIS LEACHI (Audouin, 1827)

This tick is found in the adult as well as in larval and nymphal states on carnivora, and rarely on man. It quits its host at each stage, and is an active carrier of piroplasmosis in dogs in South Africa, and may carry the virus of typhus fever in that country.

AMBLYOMMA HEBRÆUM

This is an African species widely distributed on lizards and birds (ostriches and fowls), mammalia, and man. It favours three hosts, usually of the same species. The female can lay 20,000 eggs, and in man it transmits in South Africa tick-bite fever (p. 263).

AMBLYOMMA CAJENNENSE (Koch, 1844)

This tick is of a large size and the males are adorned on the carapace with a silvery design It is found in America, from Texas in the north to Argentina and Paraguay in the south, and its natural host is the peccary. This is an important tick in South America, and it undoubtedly transmits the virus of typhus in São Paulo; under laboratory conditions, it also conveys the virus of Rocky Mountain fever (p. 263).

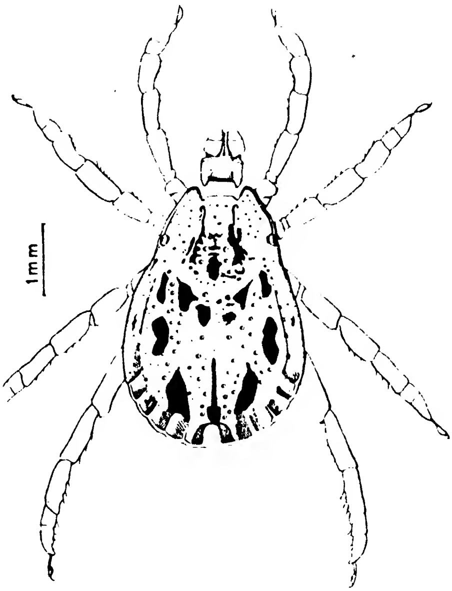


Fig. 290.—*Dermacentor andersoni*, ♂. (*Nuttall.*)

DERMACENTOR ANDERSONI (Stiles, 1908)

Synonym.—*D. venustus* (Banks, 1897).

This species is very abundant in the Rocky Mountains. The adult makes its appearance during the summer months, and is parasitic on horses, big game, and wild animals. It frequently feeds on man. (Figs. 290, 291.)

The larvæ and nymphs are found on small rodents, especially ground-squirrels, which may act as the reservoirs of the virus of Rocky Mountain fever.

The developmental cycle is as follows: The female tick, when engorged with blood, some four to six days after quitting her host, deposits 5,000–7,000 eggs. The hexapod larvæ emerge on the sixteenth day, and very shortly, within two to eight days, proceed to engorge them

selves with blood. After the larva has fallen to the ground and moulted, a nymph is produced which can survive in this state for 300 days, and this, too, after feeding, falls to the ground and moults.

The recently-developed male and female ticks are capable of fasting for two years.. When they attach themselves to their mammalian host they gradually engorge themselves with blood, and copulate four days later. After a period of eight to fourteen days the gravid females fall to the ground and deposit their eggs, while the males remain still attached to their host. Under natural conditions, when interfered with by cold weather, the whole cycle may take two years.

DERMACENTOR VARIABILIS (Say, 1821)

Synonym.—*D. electus* (Koch, 1844).

This tick is the principal vector of the spotted fever of the Rocky Mountains in the Central and Eastern portions of the United States. It may also cause canine paralysis. It is widely distributed in North America, being most abundant along the Atlantic coast. The immature

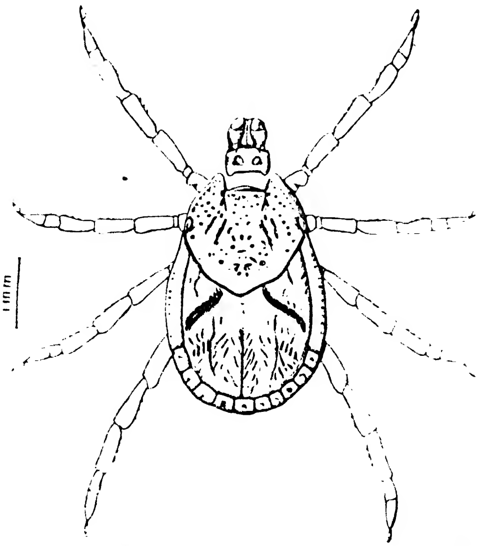


Fig. 291.—*Dermacentor andersoni*, ♀. (*Nuttall.*)

stages feed almost exclusively on small rodents, especially mice ; the adults attack dogs and other large host animals. In other respects it resembles *D. andersoni*. It usually has three hosts.

THE LINGUATULIDÆ

The Linguatulids are degenerate arachnids having neither eyes nor feet. The body is annulated, giving them a rough resemblance to a tapeworm, but Van Beneden (1848) first recognized their arthropod nature.

LINGUATULA SERRATA (Frohlich, 1789)

It is found in Southern Germany, Switzerland and Brazil.

This linguatula (Fig. 292) is found in its adult state in the nasal cavity of dogs, wolves, and foxes ; rarely in sheep or goats. The larvæ are met with frequently in the mesenteric glands of domestic animals, as well as in rabbits and hares, and have been found by Zenker, in 4·6 per cent. of autopsies, in the liver of man, in whom they appear to cause no symptoms. In Brazil it has been recorded as an intestinal parasite. The infection seems to be acquired through eating raw vegetables contaminated by the nasal secretion of dogs.

The body of the parasite is somewhat pear-shaped and flattened, and transversely striated with about 90 rings; the mouth is roughly quadrangular in shape and surrounded by hooks. The intestine is simple. The male is white, 18–20 mm. long, and measures 3 mm. broad anteriorly, 0·5 mm. posteriorly. The female, 8–10 mm. in length, is grey, but may be brown when packed with eggs; anteriorly she measures 8–10 mm. broad, posteriorly 2 mm. The eggs are ovoid, and 90 μ in length by 70 μ in breadth.

The eggs contain ripe embryos when they are deposited by the female, and pass out with nasal mucus to become attached to grass and other herbs; they are then ingested by the definitive host, penetrate the intestinal coats, and enter the viscera, the liver, lung, mesenteric glands, kidney, etc. The larva, having grown to 5–6 mm. in length, encysts, and is ingested by various carnivora, then, seized with a "wanderlust," escapes from the cyst, falls into the peritoneal cavity and even into the lumen of the intestines, and so may possibly reach the adult stage in the nasal cavities of the same host.

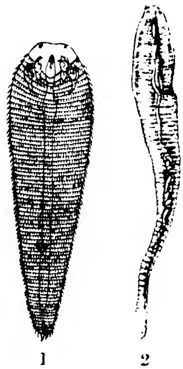


Fig. 292.—*Linguatula serrata.* (*After Brumpt.*)

1, Larval form (× 6); 2, mature form (nat. size).

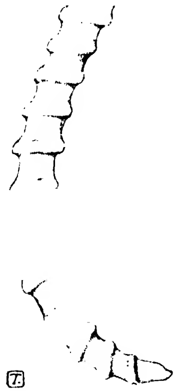


Fig. 293.—*Porocephalus armillatus.* Nat. size. (*After Sambon.*)

Porocephalus armillatus (Wyman, 1848)

Synonym.—*Armillifer armillatus.*

P. armillatus seems to be confined to tropical Africa, and hitherto, as regards man, mainly to negroes. Salm has found a porocephalus encysted beneath the serous coat of the small intestine of a Djambi native in Java.

The adult form inhabits pythons and other snakes. It has been found in *Python sebæ*, in the royal python (*P. regius*), and in the nose-horned viper (*Bitis nasicornis*). The larval—or, more correctly, the nymphal—form has been found in the lion, in the leopard, in the mandrill, in the aard-wolf, in the giraffe, in Syke's monkey (*Cercopithecus albigularis*), in the Pousargues guenon (*Cercopithecus pousarguei*), and in the African hedgehog (*Erinaceus æthiopicus*).

The body of the parasite is vermiform, yellowish, translucent, larger in females (9–12 cm. long by 5–9 mm. broad) than in males (3–4·5 cm. long by 3–5 m. broad); cylindrical in the anterior half, slightly tapering posteriorly, and terminating in a blunt-pointed cone. It is characterized by the presence of prominent opaque rings 1–2 mm. wide, numbering 16 or 17 in the males,

Radiograph of Porocephalus infection of the liver in a negro. The calcified larval parasites are encysted in the liver, where they can be recognized by their crescentic shape and cork-screw like appearance.

(Dr. Carmichael Low's case. By kind permission of Dr. Mather Cordiner.)

POROCEPHALUS INFECTION.

PLATE XXXI

18 to 22 in the females, placed somewhat obliquely and separated by inter-annular spaces 2–5 mm. wide, except between the first rings, which are faintly indicated by shallow linear furrows. (Fig. 293.) There is no clear distinction between cephalothorax and abdomen, and the rings nearest the cephalothorax are sometimes so indistinct that it is almost impossible to make out their actual number. The cephalothorax is depressed, slightly convex on the dorsal, more or less concave on the ventral surface. It is rounded anteriorly; posteriorly it is limited by the first body-rings. It varies considerably in length; its breadth is from 4 to 7 mm. The mouth, opening on its ventral surface about 1 mm. from the anterior border, is lipped by a chitinous ring. Above it are two prominent papillæ. On either side of the mouth are two protractile chitinous hooks similar in shape to feline claws. The anus is terminal at the posterior end. The genital orifice of the male is at the anterior end of the abdomen, in the middle of the ventral surface of the first body-ring; that of the female opens in the middle of the ventral surface of the caudal cone at about 1 mm. from the anus. The female is oviparous; the eggs are broadly elliptical, double-shelled, and measure 108 μ in length by 80 μ.

The nymphal form is usually found spirally coiled within a cyst, the ventral surface corresponding, as a rule, to the convexity of the curve. In shape and structure the nymph closely resembles the adult, and the number of rings is the same. Calcification of the nymphal form in the liver and other organs, may take place.

The life-history of *P. armillatus* is similar to that of the European linguatulid (*Linguatula serrata*). The eggs, disseminated by snakes harbouring the adult form, reach the intermediary host probably with food or drinking-water. That this is the probable route in man is shown by the work of Broden and Rodhain, who gave porocephalus eggs to sleeping-sickness patients, and afterwards found the nymphal forms in their livers at autopsy. After entering the stomach the larvæ penetrate the mucosa, where some remain (Fülleborn); others pass on and become encysted in almost any organ or tissue, more especially liver, mesentery, or lungs. At a certain stage of development they escape from their cysts and migrate to the serous cavities, where they cause considerable inflammation. As a rule, at this stage they are swallowed by their definitive host.

Noc and Curasson state that in *Cercopithecus* the nymphal forms take 86 days to develop, while in the definitive host (*Python sebæ*) a further 106 days are required for the parasites to reach maturity.

There is much uncertainty as to the pathogeny of this parasite. Some consider it quite harmless. There can be no doubt as to the gravity of a heavy infection at the time when the parasites are migrating in their intermediary host. In Kearney's case, reported by Aitken, twenty or thirty parasites were found encysted in the liver and one or two in the lungs. The lungs were greatly congested. In Marchoux and Clouard's case the parasites were found in the liver and in the mesentery all along the intestine, but especially about the cæcum. In Chalmers's case numerous parasites were found moving freely in the abdominal cavity over the surface of the various organs. Broden and Rodhain have found them in 33 out of 133 post-mortems on the Belgian Congo. A large number were found within the lumen of the small intestine. Many were still encysted in the lungs. Apparently when dead the parasites become cretified, when they can be demonstrated by X-rays, as in the case described by Carmichael Low (Plate XXXI).

That this worm is pathogenic to monkeys when present in large numbers was shown by Fülleborn's experiment. One monkey died after 60 days, the other 300 days, after being fed upon the tracheal mucus of infected snakes.

The diagnosis of porocephalus infection during life, except by X-ray examination, is impossible. In the Oriental region, *P. armillatus* is replaced by the closely related *P. moniliformis*, also parasitic in pythons. Several human infections have been recorded, one from Manila, one from Sumatra, and one in a Tibetan from China. *P. moniliformis* is more slender and has more rings than *P. armillatus*. The eggs are elliptical and double-shelled, about 108 μ in length by 80 μ wide. They are enclosed in a large fluid-filled circular bladder. Experimental infection can be produced by eggs kept under adverse conditions for three months.

INSECTA.

MOSQUITOES (Family Culicidæ)

The geographical range of the mosquito extends from the Arctic zone to the equator and to both hemispheres. Given stagnant or slow-flowing water and a summer temperature, this family of insects will be represented by one or many species. The distribution of particular species and the abundance of mosquitoes in any given place are determined, in addition to temperature and hydro-meteorological conditions, by various complicated circumstances.

The adult insect feeds on vegetable juices ; the males, with few exceptions, exclusively so. In addition to a vegetable diet, the females of most species when opportunity offers, suck the blood of mammals and birds. The male mosquito, not being a blood-sucker, takes no part in the diffusion of disease ; it is the female only that is a germ-carrier. (Fig. 294.)

Soon after impregnation the female lays her eggs (Figs. 295, 296, 297) from time to time—singly, in groups, or in boat-shaped masses, according to species—either on the surface of still water, on which they float, or in propinquity to water. The process of hatching out depends in great measure, as indeed do all the developmental processes connected with the mosquito, on temperature, being retarded or even suspended by cold and accelerated by warmth. In some species the eggs remain dormant throughout the winter or through a long spell of dry weather, but in ordinary circumstances the larvæ hatch out in from two to three days, and at once proceed to feed voraciously on the organic material suspended in the water. Being air-breathers, a great part of their time is passed at the surface of the water, where they lie in such a position—which varies with species—that the respiratory opening, placed near the tail, can function readily. (Figs. 298, 299.) After several moults the larva, now very much increased in size, passes to the nymph or pupa phase (Figs. 300, 301), during which it ceases to feed, and for the most part floats just awash at the surface of the water. In from one to two days the pupa-case bursts and the insect, emerging, stands on the empty case till its wings have dried, when it flies away. From first to last, from egg to imago, the process of development takes about a month in the temperature of the Italian summer ; but a much shorter time (seven to ten days) may suffice in a tropical climate. As each female mosquito may lay eggs many times in a season, and many hundreds of eggs each time, and as the young female can produce eggs within a week or ten days after her emergence from the pupa-case, it follows that one pair of insects can give rise to a large progeny in the course of a summer.

During cold weather the development of the larva is temporarily sus-

pended, and the surviving adults, at all events the females, hibernate in dark and sheltered places, to become active again on the return of warm weather. In this way the species is carried over the cold weather of winter,

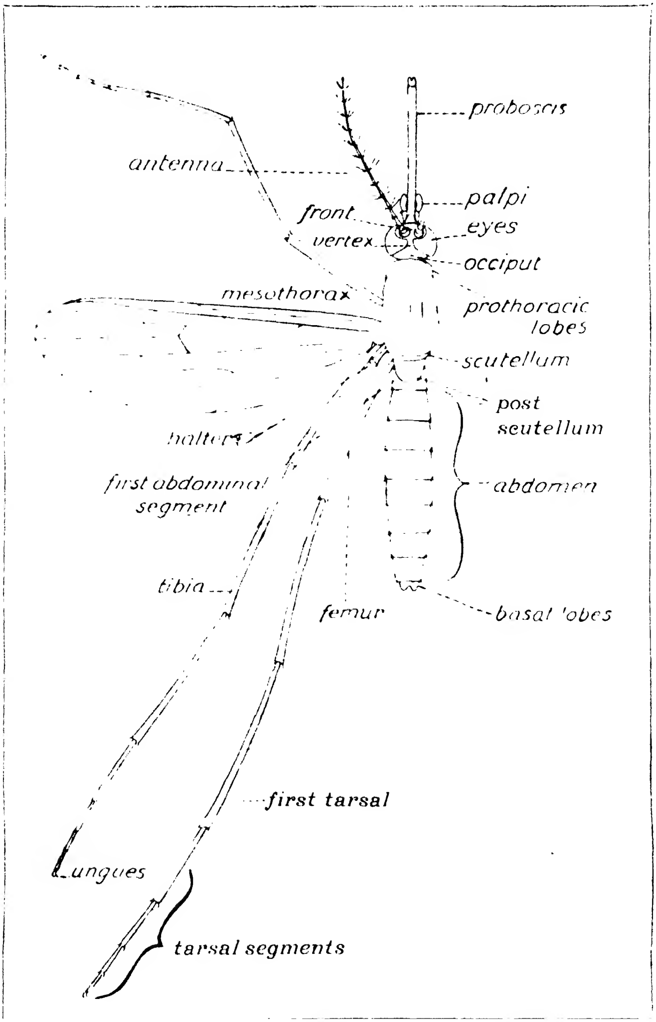


Fig. 294.—Female mosquito, to show anatomy.

though there are some that hibernate in the larval stage and others in the egg. The duration of the life of the adult insect has not been definitely ascertained; it is known that some species, if supplied with water and suitable food, can live for several months.

It is suggested that, to deposit her own eggs, the mosquito tends to return to the particular pool in which she herself was hatched out, and that she rarely strays from the vicinity more than a few yards, quite exceptionally beyond half a mile. Occasionally she may be blown for some distance by

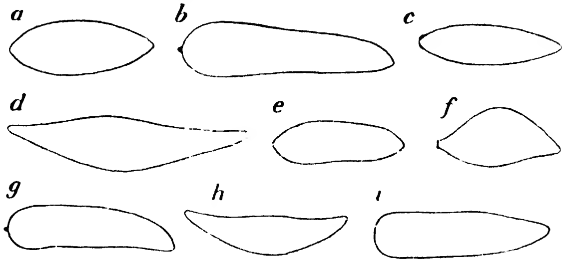


Fig. 295.—Various forms of mosquito eggs.

a, *Grabhamia dorsalis*; *b*, *Culex pipiens*; *c*, *Culex scapularis*; *d*, *Mansonia titillans*; *e*, *Aedes ægypti*; *f*, *Tæniorhynchus fulvus*; *g*, *Culex fatigans*; *h*, *Janthinosoma lutzi*; *i*, *Tæniorhynchus fasciolatus*.

gentle winds; and it is believed that in certain circumstances, probably connected with food supply and overstocking, she will travel singly or in vast swarms for long distances. Such migrations, however, are quite unusual. Of course, mosquitoes may be, and often are, transported great distances in ships, railway carriages, and similar vehicles, and in this way man aids

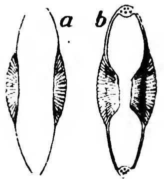


Fig. 296.—Eggs of *Anopheles maculipennis*.

a, Under side; *b*, upper side.

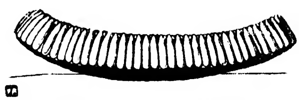
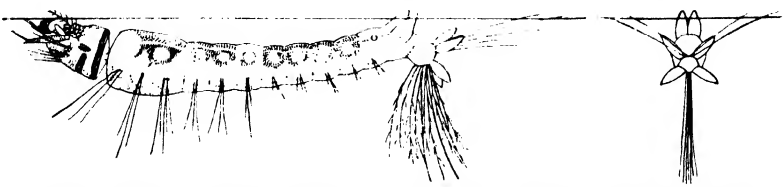


Fig. 297.—*Culex fatigans* **egg-boat.** (*After Sambon.*)

in their diffusion; but for the most part the mosquito is a feeble and timid flyer, disliking to leave her accustomed haunt, and seldom rising high above the ground. So soon as even a moderate breeze springs up, she seeks shelter in bush, or house, or cranny. Some species are domestic; others live ex-



ig. 298.—Larva of *Anopheles maculipennis* **Meigen, showing breathing position at surface of water.** (*After Howard, "Bull. United States Dept. Agr."*)

clusively in jungle or forest; some, after passing the day in the open, visit human habitations or the haunts of birds and beasts during the night. The great majority of species are nocturnal in habit, although many of these can be coaxed into activity by the reproduction of night-like conditions of shade and atmospheric stillness.

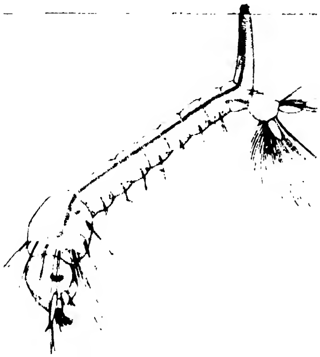


Fig. 299.—Larva of *Culex fatigans* **in breathing position at surface of water.** (*After Howard, "Bulletin United States Dept. Agr."*)

Fig. 294 gives a good idea of the leading features of the anatomy of the mosquito and of the names applied to the various parts and organs, and will help the student to understand descriptions of genera and species. For distinctions based on scale characters, *see* Figs. 307–9.

The antennæ of the male insect (Figs. 302, *a*, and 303, *a*) are usually adorned with a profusion of long, silky hairs, in marked contrast to the

Fig. 300.—Pupa of *Anopheles maculipennis.*

Fig. 301.—Pupa of *Culex fatigans.*

scanty, down-like, and short hairs on the antennæ of the female; this is an easily recognized indication of sex in most species.

The proboscis consists of a number of piercing elements enclosed in a sheath—the labium, which, at its free end, is tipped with two minute labella. In feeding, the mosquito raises her hind-legs and presses the tip of the proboscis against the skin. This causes the labella (Fig. 304, *h*) to splay out

and so serve as a support to the piercing elements—namely, the labrum, hypopharynx, mandibles, and maxillæ (Figs. 304, 305)—which are now thrust into the skin. The labium does not penetrate; as the stabbing elements sink into the skin the proboscis sheath bends backwards about its middle,

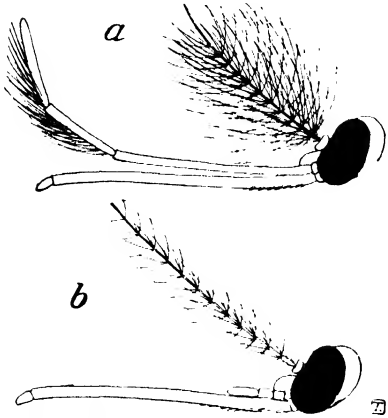


Fig. 302.—Heads of Culicini.
a, Male; *b*, female.

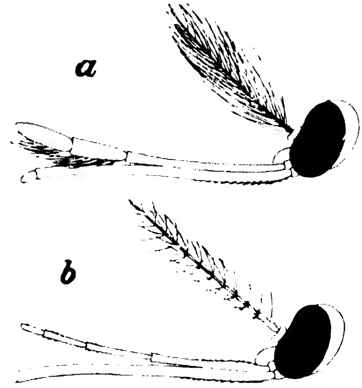


Fig. 303.—Heads of Anophelini.
a, Male; *b*, female.

the labella still pressing against the skin and clasping the stylets. The secretion of the salivary glands passes along the salivary duct, and thence down a minute canal which traverses the hypopharynx to its tip, and so into the subcutaneous tissues of the bitten animal. It is supposed that the

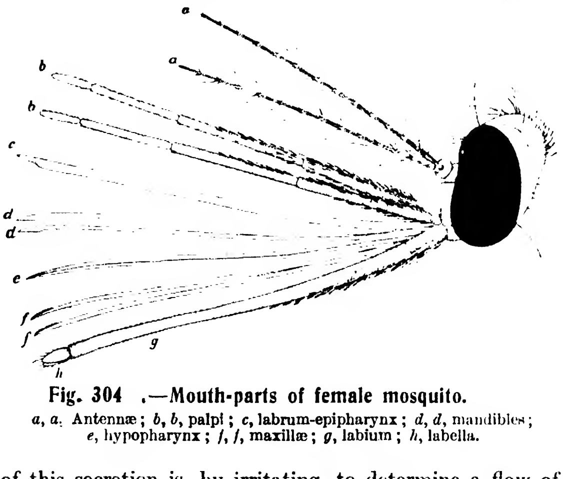


Fig. 304.—Mouth-parts of female mosquito.
a, *a*, Antennæ; *b*, *b*, palpi; *c*, labrum-epipharynx; *d*, *d*, mandibles; *e*, hypopharynx; *f*, *f*, maxillæ; *g*, labium; *h*, labella.

function of this secretion is, by irritating, to determine a flow of blood to the part bitten, and also prevent coagulation of the blood. To many people this secretion is a powerful irritant, although repeated inoculation tends to produce tolerance, as in the case of many other poisons.

A buccal tube is formed by the apposition of the upper surface of the hypopharynx to the under-surface of the labrum (Fig. 305). Along the tube so formed the blood is aspirated by the expansion of the gizzard-like organ, and then driven by the contraction of the same into the stomach, or middle intestine as it is called. A mosquito will fill herself in a minute or thereabouts. She then withdraws her proboscis and flies heavily away

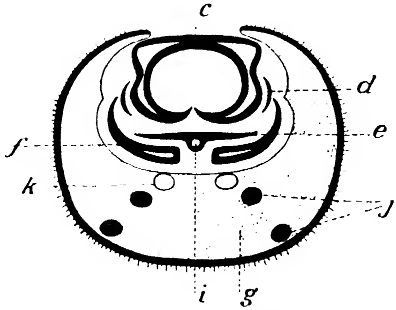


Fig. 305.—Section of mosquito's proboscis.
(*Adapted from Nuttall and Shipley.*)

c, Labrum-epipharynx; *d*, mandible; *e*, hypopharynx; *f*, maxillæ *g*, labium; *i*, salivary duct; *j*, muscles; *k*, trachea.

to some sheltered spot to digest the meal. Apparently the first step in digestion is the concentration of the blood she has imbibed; this is effected by excretion of the watery portion of the liquor sanguinis. Often while this process of dehydration is proceeding, even while she is sucking, droplets of clear fluid may be seen ejected at her anus. The concentrated blood becomes in this way a viscid tarry mass, which is gradually, in the course of

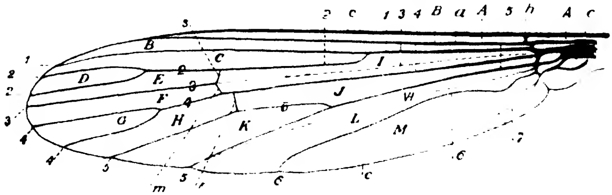


Fig. 306.—Wing of *Culex* (male), to illustrate terminology.

c, Costa; *a*, auxiliary vein; 1–6, first to sixth longitudinal veins and branches; 7, seventh or false (unscaled) longitudinal vein; *VI*, unscaled vein between fifth and sixth longitudinal veins; *h*, humeral transverse vein; *s*, supernumerary transverse vein; *m*, middle transverse vein; *p*, posterior transverse vein; *A*, costal cells; *B*, subcostal cells; *C*, marginal cells; *D*, anterior fork cell or first submarginal cell; *E*, second submarginal cell; *F*, first posterior cell; *G*, hinder fork or second posterior cell; *I*, first basal cell; *J*, second basal cell; *K*, anal cell; *L*, axillary cell; *M*, spurious cell.

three or four days, partly absorbed, and partly voided as gamboge-coloured fæces. The mosquito is now ready for another meal.

The rich pabulum supplied by blood seems to favour ovulation.

Many kinds of insect possess blood-sucking propensities. As a rule there is little difficulty in distinguishing most of these from the mosquito. There are certain diptera, however, which closely resemble the latter in their appearance as well as in their habit. These the student should learn to distinguish.

The principal of the mosquito-like blood-suckers are the Midges (Chironomidæ) and the Sandflies (*Phlebotomus*). The following are the diagnostic points :

Mosquitoes have a long suctorial proboscis, and the veins of their wings are fringed with scales. (Fig. 306.)

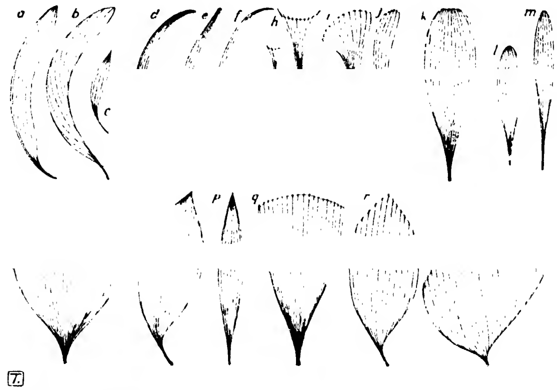


Fig. 307.—Graphic key to distinctions based on scale characters.

b, *c*, Narrow curved scales ; *d*, *e*, *f*, hair-like curved scales ; *g*, *h*, upright forked scales ; *i*, *j*, long, twisted scales ; *k*, large lanceolate scale ; *l*, *m*, small narrow lanceolate scales ; *n*, large expanded scale ; *o*, *p*, spindle-shaped scales ; *q*, broad flat scale ; *r*, *s*, broad irregular scales.

Midges (*Chironomidæ*) are very slender and minute, have a short suctorial apparatus, and their wings are devoid of scales. (Fig. 324, p. 1000.)

Sandflies (*Phlebotomus*) are small, slender, and very shaggy ; have a comparatively short suctorial apparatus, comparatively long legs, narrow, pointed, hairy wings, and long, hairy antennæ. (Fig. 321, p. 997.)

Most authorities separate the Culicidæ into two subfamilies, namely

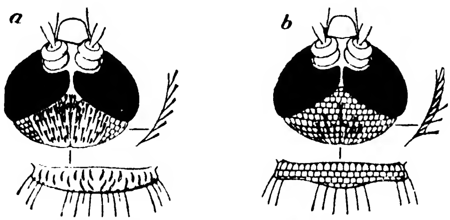


Fig. 308.—Various types of "scale vestiture."

(*Such scale characters are now regarded as specific and not of generic importance.*)

a, *Anopheles*, head, scutellum, and lateral view of head scales ; *b*, *Aëdes* (*Stegomyia*) *ægypti*, head scutellum, and lateral view of head scales.

—(1) Corethrinæ, in which the proboscis is short and not formed for piercing ; (2) Culicinæ, or typical mosquitoes with elongate proboscis. The Culicinæ, again, are arranged in four natural tribes.

Genus Anopheles Meigen (Plate II, facing p. 58)

Head only moderately broad, usually covered with upstanding forked

scales, though scales of other kinds are also present in a few species. (Figs. 307–11.) Maxillary palps long and spatulate in the male ; as long as, or not much shorter than, the proboscis in the female. Free edge of scutellum simply convex, not trilobate ; post-scutellum bare. Abdomen either sparsely hairy or with localized patches of scales ; sometimes with a considerable expanse of scales, which, however, never form a uniform, complete, and

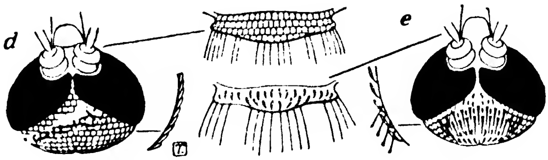


Fig. 309.—Continuation of Fig. 308.
Megarhinus, head, scutellum, and lateral view of head scales ; *e*, *Culex*, head, scutellum, and lateral view of head scales.

compact investment. Wings commonly dappled or profusely speckled, but occasionally quite spotless. Legs remarkably elongate (Figs. 310, 311). In repose the body is usually inclined at an angle with the resting surface (*see* Figs. 313, 314).

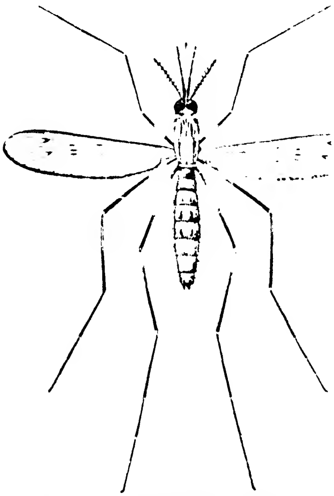


Fig. 310.—*Anopheles maculipennis*, **female.**

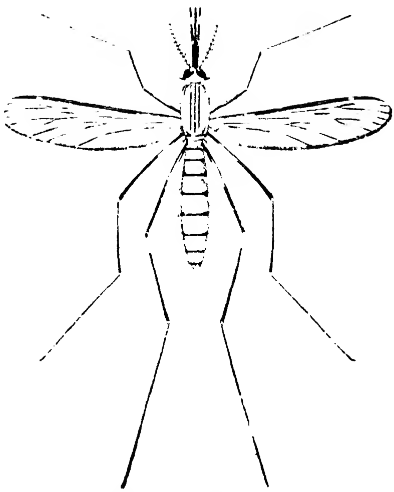


Fig. 311.—*Anopheles funestus*, **female.**

The eggs are boat-shaped, and with rare exceptions have their investing membrane inflated laterally to form a pair of floats. (Fig. 296.)

The larva has the head at least as long as broad, and has four bristles or feathered hairs projecting from the free edge of the clypeus. The long lateral hairs of the thorax and abdomen are strongly feathered. Some or all of the abdominal segments, as far as the seventh, carry dorso-laterally a pair of characteristic rosettes or cockades of scales. The breathing openings

are situated in a hollow on the dorsum of the eighth segment, the hollow being bounded laterally and posteriorly by a system of folds or valves, whereby the larva assumes a horizontal position. (Fig. 298.)

The larvæ occur, not only in all kinds of stagnant water, but also in pools in the beds of rivers and mountain streams, or even in the current if there are also floating weed and debris for their protection, in domestic water-vessels, and, occasionally, in the water that collects in holes in trees; some species thrive in brackish or salt water, and each species has its own particular kind of habitat.

As regards the capabilities of any particular species of anopheline as a factor in the transmission of malaria, it is necessary that one should ascertain, as Swellengrebel, Schüffner and de Graaf have pointed out, whether the species occurs in numbers; whether the parasites of malaria can complete their development in its body; whether it habitually feeds in nature on human blood; whether it feeds in the jungle or visits man in or near his dwelling places: what is the vegetable food of the female; and whether this

Fig. 312. — Resting position of *Culex fatigans*.

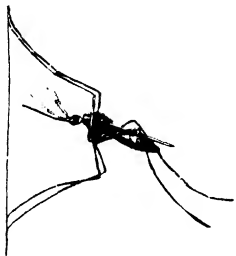


Fig. 313.—Resting position of *Anopheles hyrcanus*.

Fig. 314.—Resting position of *Anopheles maculipennis*.

substance interferes with the development of the malaria parasites. One of the points recently brought out is that a species proved to be a natural carrier of malaria in one situation sometimes does not appear to play an important part in another. Thus *A. aconitus* has proved to be a good carrier of malaria experimentally, and has been found naturally infected in Malaya and Western Java, yet in another part of the East Indies over 1,000 specimens have been dissected with negative results. Again, in North America *A. crucians* is found to be an effective carrier only when bred in brackish water. Again, *A. rossi* plays little or no part in the transmission of malaria, but yet on occasions during the height of an epidemic it has been found to be infected in Java to the extent of 8·6 per cent. But even there this species plays a minor part.

Anopheles maculipennis (Fig. 310) is the best-known malaria-transmitting species all over the world. It is nocturnal in its habits and is most active between 12 midnight and 2 a.m. This species indulges in a peculiar marriage-flight which appears to be essential for the propagation of the species; constant changing of their resting-places appears to be indispensable to their existence so that the anopheles population of any spot becomes entirely changed in a few days.

It has become sufficiently clear, as the result of the work of Hackett and Missiroli, that *A. maculipennis* is not a monogeneous species, but a collection of widespread varieties. Those generally accepted are :

A. maculipennis, Meigen, or *typicus*, which lay eggs with two simple bars ; *A. m. messiæ*, Falleroni, which lays dark eggs and barred ; *A. m. melanoon*, Hackett, which lays uniformly black eggs ; *A. m. atroparvus*, Van Thiel, which lays a dark grey and dappled egg ; *A. m. labranchiæ*, Falleroni, which lays a light grey and dappled egg ; and *A. m. elutus*, Edwards, which lays a uniformly grey egg.

These varieties are identified by the markings of the eggs and character of the floats, by the character of the larval hairs, and by the external harpaginal spine of the adult male. Authorities are of the opinion that the egg-types provide the only satisfactory method of dividing *A. maculipennis*.

As regards geographical distribution, *A. maculipennis typicus* is found in England, Norway, the Black Forest and the Hartz Mountains ; *messiæ* in the fresh waters of Europe, its southerly range being Italy and the Balkans ; *melanoon* favours the rice-fields of North Italy and South-East Spain ; *atroparvus* is a salt-water breeder on the North Coasts of Europe ; *elutus* replaces *atroparvus* in the south ; *labranchiæ* takes the place of *atroparvus* in North Italy and is the dominating variety in the Campagna.

The subdivisions of *A. maculipennis* are supported by biological differences in breeding-places, sexual behaviour, and habits. *Atroparvus* breeds in saline water, *messiæ* in fresh. *Atroparvus* does not go into complete hibernation. All varieties are equally susceptible to malarial infection, and although some prefer to feed on animals, there is never any insurmountable barrier. In almost the whole of northern Europe *A. maculipennis* lives on domestic animals, and man is protected from malaria by the deviation of Anopheles by animals. In the malarious regions of southern Europe *maculipennis* bites man persistently. The principal reason for differences in behaviour in the north and south, is that the anopheles population of the latter region consists of varieties—*labranchiæ* and *elutus*—which feed upon man. The races *typicus* and *melanoon* are rarely associated with malaria. *Messiæ* is deviated by animals and goes completely into hibernation in winter. It has now come to be recognized that *A. occidentalis* Dyer and Knab, is identical with *A. maculipennis*, and has the same biological varieties. It occurs along the northern borders of the United States, and in southern Canada, dipping in a southerly direction along the Pacific coast into Mexico.

Sinton and Shute, in a report upon the longevity of mosquitoes in relation to the transmission of malaria in nature, obtained no evidence that, among healthy specimens of *A. maculipennis* var. *atroparvus* infected with *Plasmodium vivax* and kept under conditions favourable to longevity, there is any noteworthy decrease in life as the result of the plasmodial infection. There is some evidence that severe plasmodial infections may exert some deleterious action, but this is so slight as to be only detectable in insects which are weakly or debilitated from some other cause.

Although evidence which is available adds little support to the suggestion that plasmodial infections may be a serious cause of mortality amongst anopheline mosquitoes in nature, especially in the case of *A. maculipennis*, var. *atroparvus*, it does not offer any satisfactory explanation as to the reason why some anophelines are important as malaria-carriers under natural conditions, while others are not.

Species known to carry the Malaria Parasite

Europe.

A. bifurcatus. B.T. and M.T.
A. hyrcanus. B.T., M.T. and Q.
A. hyrcanus var. *pseudopictus.* B.T., M.T. and Q.
A. maculipennis. B.T., M.T. and Q.
A. plumbeus. B.T. and M.T.

Asia.

A. aconitus. M.T.
A. barbirostris. B.T. and M.T.
A. bifurcatus. B.T. and M.T.
A. culicifacies. B.T., M.T. and Q.
A. elutus (*sacharovi*). (Palestine.) B.T. and M.T.
A. fuliginosus. B.T., M.T. and Q.
A. hyrcanus var. *sinensis.* (China.) B.T.
A. hyrcanus var. *nigerrimus.* (India and Malaya.) B.T., M.T. and Q.
A. hyrcanus var. *peditæniatus.* (Malaya.) B.T., M.T. and Q.
A. hyrcanus var. *argyropus.* (Dutch E. Indies.) B.T., M.T. and Q.
A. kochi. B.T. and M.T.
A. leucosphyrus. B.T., M.T. and Q.
A. listoni. B.T., M.T. and Q.
A. ludlowii (*A. sundaicus*). B.T., M.T. and Q.
A. maculatus. M.T.
A. maculipalpis. M.T.
A. maculipennis. B.T., M.T. and Q.
A. minimus. M.T.
A. multicolor. M.T.
A. punctulatus var. *moluccensis.* B.T. and M.T.
A. stephensi. B.T., M.T. and Q.
A. superpictus. B.T. and M.T.
A. tessellatus. M.T.
A. umbrosus. B.T. and M.T.
A. vagus. B.T. and M.T.
A. willmori. B.T.

Africa.

A. bifurcatus. B.T. and M.T.
A. funestus. M.T. and Q. (Fig. 311.)
A. gambiæ (formerly *costalis*). M.T. and Q.
A. multicolor. M.T.

North America.

A. crucians. B.T. and M.T.
A. punctipennis. B.T. and M.T.
A. quadrimaculatus. B.T. and M.T.

South America.

A. albimanus. B.T. and M.T.
A. albitarsis. B.T. and M.T.
A. argyritarsis. B.T. and M.T.
A. crucians. B.T. and M.T.

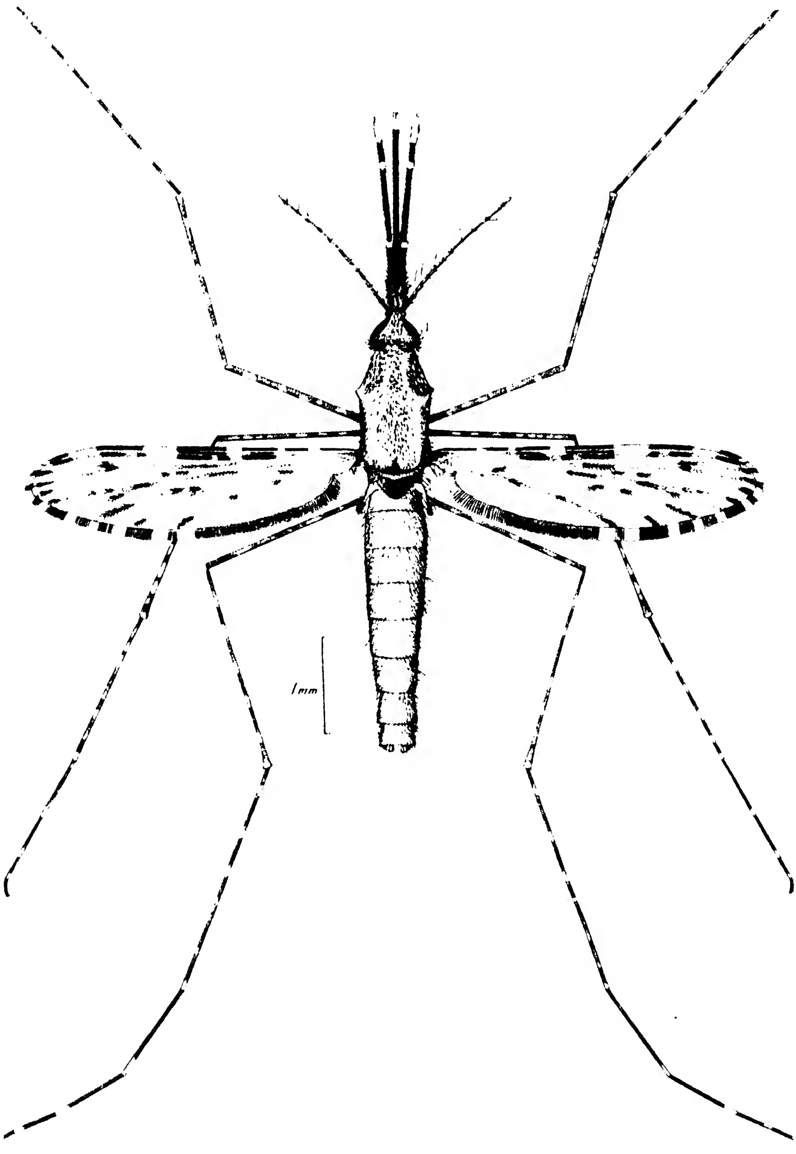


Fig. 315.—*Anopheles gambiæ* (*Giles*). (*McKay*).

SOUTH AMERICA (*continued*).

A. gambiæ. (In 1930 this species was found breeding abundantly in Natal, Brazil—apparently having been transported from West Africa[1].) (Fig. 315.)
A. pseudopunctipennis. M.T.
A. punctipennis. B.T. and M.T.
A. tarsimaculatus. M.T.

AUSTRALIA.

A. annulipes. (?)
A. punctulatus. M.T.
A. punctulatus var. *moluccensis.* B.T. and M.T.

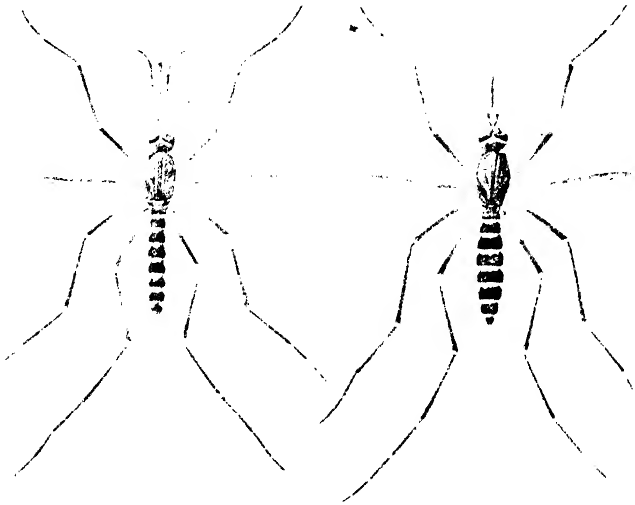


Fig. 316.—***Culex fatigans*, male and female.**
(*After A. Eysell, Mense's "Handbuch der Tropenkrankheiten," 3rd edit.*)

CULEX FATIGANS (Wiedemann, 1828) (Fig. 316)

Synonyms.—*C. skusei* (Giles, 1890); *C. quinquefasciatus* (Say, 1823).

This is a nocturnal species—often incorrectly mistaken for *C. pipiens*, but it is a denizen of the tropics and subtropics, and is commonly found in human habitations; it is, in fact, a domestic species and breeds in water-tubs or in any collection of stagnant water. The adult can be distinguished from anopheles by the erect position it assumes on resting (Fig. 312.)

[1] *Anopheles gambiæ* (*A. costalis*) is the principal carrier of malaria in Algeria, Morocco, Southern Arabia and, especially, the West Coast of Africa from the southern border of the Sahara, south to the Zambesi River. It is widely distributed throughout Central Africa. In 1930 the species crossed the ocean, apparently carried by aeroplane or on one of the fast French destroyers which at that time were working in connection with the French air lines between Dakar in West Africa and Natal in Brazil. This species was first discovered within the limits of that city. The seriousness of its presence was recognized and it was hoped that the invasion might be localized, but the species has continued to spread inland aided by the prevailing winds, and by 1931 it had travelled up the coast for 115 miles. In recent years, severe epidemics of *gambiæ*-conveyed malaria have occurred in localities over 200 miles west and north of Natal. In one valley of the State of Ceara alone there were over 50,000 cases of malaria in 1938.

Its chief claim to interest is the fact that this species was first discovered by Manson in 1879 to be the intermediary host of *Wuchereria bancrofti*, and was suspected to be the transmitter of the virus of dengue by Graham in 1903.

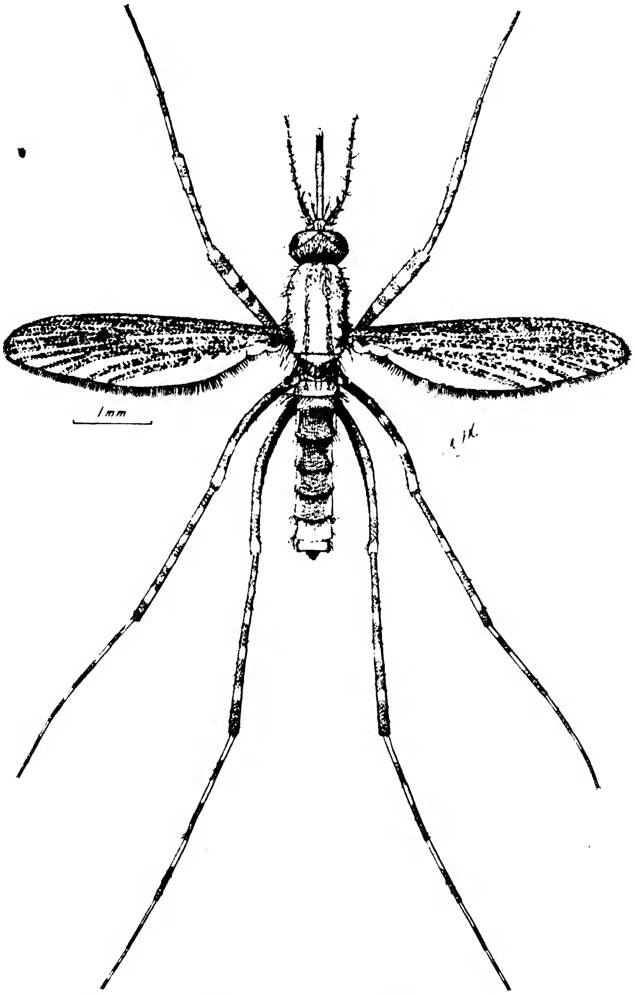


Fig. 317.—*Mansonioides annulifera* (*Theo.*) ♀ (*McKay.*)

The mosquito also acts as intermediary for the filaria of the dog, *Dirofilaria immitis*, and the *Proteosoma* of birds. A description of eggs and larvæ is given at pp. 980, 981.

CULEX PIPIENS (Linn., 1758)

This mosquito is widely distributed in temperate regions. It is a domestic and nocturnal species, breeding in any collection of stagnant or semi-stagnant water.

63

It is now known to transmit *W. bancrofti* in China. *C. pipiens* differs mainly from *fatigans* in the characters of the male genitalia, but in its habits it is very similar.

Marshall has now shown that two distinct species have been confused under the designation *pipiens*; this name should be retained in the man-ignoring form, *molestus* being used for the man-biting form.

MANSONIA (TÆNIORHYNCHUS) (Edwards)
SUBGENUS MANSONIOIDES (Fig. 317.)

Members of this genus occur in tropical and Central America, throughout tropical Africa, and in Asia, especially Malaya. They are less important in temperate North America, Europe, and Australia. These mosquitoes are recognizable by the very broad asymmetrical wing scales, which are of two colours, white and grey, like salt and pepper, but which do not make conspicuous pale and dark areas. The palpi of the male are longer than the

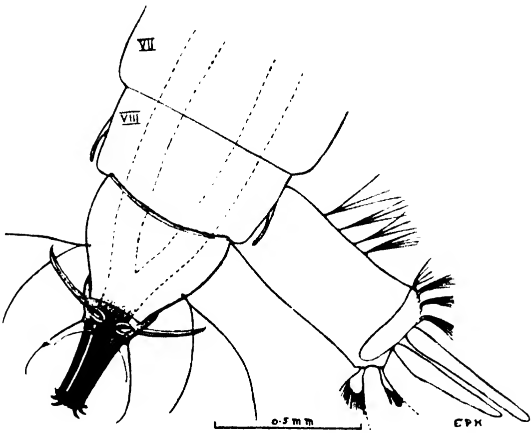


Fig. 318. Respiratory syphon and terminal segments of larva (dorsal view) of *Mansonioides*.

(From Bulletins from Inst. for Medical Research, Federated Malay States: Endemic Filariases in the F.M.S. (Poynton and Hodgkin)).

proboscis; the penultimate segment is turned upwards, while the last segment is minute and is turned downwards. The end of the abdomen of the female curves upwards, so that only six and a half segments are visible dorsally. The eighth segment is entirely retracted, is of a peculiar form, and carries a row of strongly chitinized teeth on the tergite. The arrangement of these teeth and the shape of the lobes of the sternite are of value in identification. There are five species of importance which are concerned with the transmission of *W. bancrofti* and *Filaria malayi*, *M. annulatus*, Leic., *M. annulifera* (Theo), *M. indiana*, Edwards, *M. longipalpis*, v. d. Wulp, and *M. uniformis* (Theo).

The larvæ of Mansonia are readily recognizable by the peculiar form of the respiratory syphon, which is adapted for piercing plant tissues (Fig. 318). This structure is short, and has a conical base and a distinctive black tip made up of several parts, one of which has a saw edge and ends in a ring of retractable hooks. The known larvæ of Mansonia closely resemble one another. The pupæ are also distinguishable by the form of the respiratory horns which,

like the syphon of the larvæ, are modified for piercing plant tissues (Fig. 319). Each horn is long and terminated in a narrow, strongly chitinized portion, which bears a pair of feather-like structures and ends in a sharp point. All species of Mansonia are known to be man-hunters and fierce biters, and to attack either in or out of doors. Primarily night-biters, in the jungle they feed at any time. The eggs are laid in small batches, containing a hundred or more, on the underside of leaves of water plants just above the surface of the water. The most characteristic peculiarity, and the one which defines the distribution of the genus, is the habit of the pupæ and larvæ of obtaining air from the submerged portions of water plants.

The larva of Mansonia forces its respiratory syphon into the air-containing tissues, and remains there till forcibly removed. The pupa does likewise. The roots appear to be the part of the plant most favoured. Different species have preference for certain water plants, and the type of water in which they prefer to breed. *M. annulifera*, *M. indiana*, and *M. uniformis* are most easily found among the roots of water plants floating and growing in exposed situations, especially *Pistia stratiotes*, a plant which floats with hanging roots in still water. The food of the larvæ consists of fine particles of organic matter which are freed from coconut husks in the process of coil and rope-making.

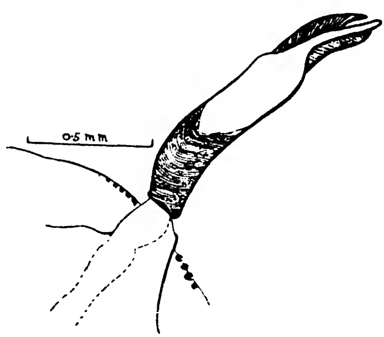


Fig. 319.—Respiratory horn of pupa of *Mansonioides*.

GENUS AEDES (Meigen, 1818)

The members of tropical interest of this genus are those mosquitoes which were formerly described as *Stegomyia* by Theobald, and are still widely known under that name. They are mostly black-and-white insects with white, silvery, or yellow lines, bands, or spots on the thorax and legs. In India they are known as " tiger mosquitoes," on account of their striped appearance. They seem to have a decided preference for the littoral, and certain species (*A. ægypti*, *A. albopictus*) are frequently found on ships, and are no doubt distributed by these means. At present the subgenus *Aedes* (*Stegomyia*) includes many species which are identifiable by their striking thoracic and other ornamentation.

The distinctive characters are : In the female the palpi are short : in the male they are usually longer than the proboscis, the last two joints being upturned and sparsely haired. The vertex is covered with broad, flat scales with a few or no narrow scales on the nape. The thorax is usually conspicuously ornamented, while the eighth abdominal segment in the female is large and retractile.

The *eggs*, instead of being cemented in rafts, are deposited separately, each being surrounded by small air-chambers. They are capable of withstanding a considerable degree of desiccation. The *larvæ* maintain an almost vertical attitude in water. They have short, smooth antennæ, with not more than three hairs in a shaft tuft. The frontal hairs are single ; the siphon is short, not much more than twice as long as broad. The hair-tuft is situated about the middle of it, and the comb teeth occur in a single row.

Aëdes ægypti

Synonyms.—*A. argenteus; Stegomyia fasciata* (Fabr., 1805); *Culex ægypti* (Linn, 1762).

A. ægypti (Plate IX, facing p. 354) can be recognized by the peculiar lyre-shaped ornamentation of its thorax—two dull-yellow parallel lines in the middle and a curved silvery line on each side. The proboscis is not banded; the abdomen is banded basally; the last hind tarsal joint is all white, and some of the other tarsal joints are marked by light bands basally. This widely distributed species is essentially a domestic form, and bites with avidity. It breeds in small artificial collections of water, such as barrels, puddles, cisterns, sagged rain-gutters, and even in such small receptacles as sardine-tins; the nature of the water appears to be a matter of indifference. The eggs resist a considerable degree of desiccation, and, as they may sink to the bottom of the water in which they lie, they are readily pumped into water-tanks of ships, and may even be dried and remain viable when placed in an envelope and sent through the post from far-off Africa and Central America. This species transmits the virus of yellow fever and that of dengue (Bradley and Macdonald).

Although widely distributed, *A. argenteus* does not occur abundantly in certain parts, such as Australia, the Malay States, China, Africa, and the West Indies, where its place is taken by other species which greatly resemble it. Under experimental conditions in West Africa, Bauer and Philip have found other West African mosquitoes can transmit yellow fever to monkeys; such are *A. vittatus* (*sugens*), *A. apicoannulatus*, *A. africanus*, *A. simpsoni*, and a related genus—*Eretmopodites chrysogaster*.

Aedes (Stegomyia) albopictus (Skuse, 1895)

Synonym.—*Stegomyia scutellaris.*

A very common and widely distributed species in the East, where it breeds in artificial receptacles in the vicinity of dwellings, as well as in tree-holes, bamboos, etc. Is said to be the transmitter of dengue fever in Japan (Yagamuchi, Koizumi, and Tonomura). The development of *W. bancrofti* in this mosquito is arrested about the seventh day. In general habits it resembles *A. ægypti.* It is easily distinguishable from that species by the single broad median stripe which adorns the scutum. (Fig. 320, A.)

Aëdes (Stegomyia) variegatus (Doleschall, 1858). (Plate IX, facing p. 354)

Synonym.—*Stegomyia pseudoscutellaris* (Theobald).

This species is widely distributed in the Pacific islands, where it replaces *A. albopictus.* It occurs also on Christmas Island and in New Guinea, and the Editor originally demonstrated that it acts as the chief transmitter of the non-periodic filaria (*W. bancrofti*) of those regions. In fact its distribution and that of the non-periodic filaria coincide. It is diurnal in habit, and may be distinguished by three parallel white stripes on the mesothorax and incomplete white abdominal cross-bands (Fig. 320, B). The larva resembles that of *A. ægypti,* from which it can be distinguished by lateral barbs of the comb scales which are distinctly smaller and more delicate than those of *A. ægypti.* The breeding-places of this insect are peculiar. It is not in any way a domestic

species like the preceding; its main requirements are small collections of fresh water containing decayed vegetable matter—in husks and shells of coco-nuts; in crevices and holes in trees; in the artificial reservoirs hewn out of coco-nut trees and used as wells by the Pacific islanders; in holes in coca-pods gnawed out by the Pacific rat; in bottles and tins which may be lying about in sheltered spots in the bush.

Both larvæ and pupæ can exist for a long time at the bottom of these breeding-places after the water has evaporated.

This species is extremely intolerant of sun and wind; its main haunt is the still, shady, thick bush round native villages. It is strictly a day-biting species.

Phlebotomus (Sandflies)

These are minute and very hairy flies, from 1·5 to 2·5 mm. in length, and are easily recognizable. Only the females suck blood, and in some people their bite causes a considerable local disturbance; in others, little or none.

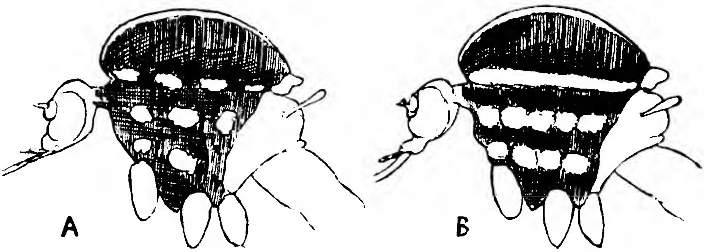


Fig. 320.—Diagrammatic representations of marking on thorax of (A) *Aëdes albopictus* and (B) *Aëdes variegatus*—lateral views.

These insects carry several diseases, notably phlebotomus fever (p. 403): there is also good reason for suspecting that they act as the carriers of leishmania of oriental sore and kala-azar (pp. 197, 174). *P. verrucarum* was believed by Townsend to transmit the virus of Oroya fever (p. 243) in the Andes.

The **geographical distribution** of the sandflies in the tropics and subtropics is a wide one. *P. papatasii* has been taken as far north as Paris (Langeron), and occurs throughout Southern Europe, especially in Italy and Dalmatia, in the Mediterranean basin, in North and East Africa, as well as in Java and India.

The greater part of the body is covered with long, yellow "hairs," among which there may be patches of scales. The antennæ have 16 joints. The proboscis is comparatively short; it is as long as the head, and contains a number of piercing organs.

The wings are definitely pointed; on removal of the outer "hairs" the venation can be distinctly seen. The legs are long and slender, and the abdomen is divided into 10 segments.

In the *female* the abdomen is spindle-shaped, and is provided with an upper and a lower pair of small claspers. In the *male* there are four pairs of sexual appendages—the upper and lower claspers and various other

structures known as "submedian lamellæ," "intermediate appendages," and "the intromittent organ" (Newstead). (Fig. 321.)

While feeding, *Phlebotomus* is easily disturbed, the slightest movement of the skin being sufficient to put it to flight. It thrusts the somewhat stout rostrum downwards, while the maxillary palpi diverge a little. Blood can be seen entering the stomach within 60 seconds of haustellation.

Life-history.—Considerable moisture is apparently necessary to induce oviposition. The eggs, which are laid singly, are 0·385 mm. in length by 0·12 mm. in breadth, and are thinly covered with a viscous substance. (Fig. 322.) A few hours after being laid they become darker in colour. Six to nine days after deposition they hatch into 12-segmented, caterpillar-like larvæ, characterized by two very long dorsal bristles on the terminal segment.

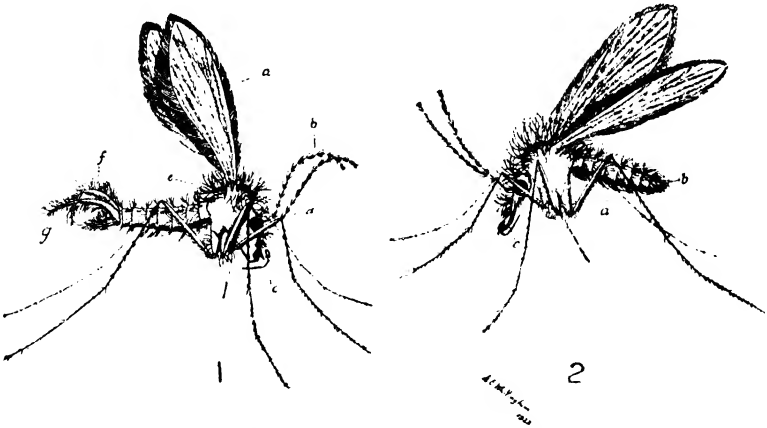


Fig. 321.—*Phlebotomus papatasii.* × 10.
(*After Whittingham, "Brit. Med. Journ."*)

1. Fully developed male imago. *a*, Hairy wings ; *b*, antennæ ; *c*, labial palps *d*, eye halteres; *f*, claspers ; *g*, genital spines.
2. Fully developed female imago. Body hairs arranged in tufts; abdomen (*a*) spindle-shaped; *b*, ovipositors ; *c*, proboscis.

Each segment bears a number of spines arranged in a transverse row. The head is armed with formidable large and dentate mandibles, which are at first white, but afterwards become dark brown. (Fig. 322, *2*.) The newly hatched larva is sluggish, lies flat, with caudal bristles extended in the same plane, and progresses by slow undulating movements. It commences to feed on decaying nitrogenous material—it may be the bodies of defunct parent flies or the dejecta of lizards. The duration of the larval stage varies considerably, but in favourable circumstances the larval life of *P. papatasii* is about four weeks. According to Whittingham, there are four distinct stages in the larval life, with a complete moult between each. The first instar lasts on an average seven days, and is characterized by an egg-tooth on the dorsum of the head ; the second instar occupies about five days, the third the same period, during which the terminal segment becomes pigmented (Fig. 322, *3*) ; the fourth, about nine days in Malta, where the whole life-cycle takes seven to eight weeks in July and August, with a mean daily

humidity of 50–60 per cent. (Fig. 322, *4*.) According to Roubaud these insects are heterodynamic, *i.e.* they do not all develop in the same manner as do many other flies; some individuals remain in the larval state for considerable periods, and hibernation probably always takes place in the larval state.

The pupa is ochreous-buff in colour, and bears the thoracic appendages free from the body; the integument is covered with minute squames, and small spines are present on the sides of the thorax and abdomen. In Malta the duration of the pupal stage is about nine days. The imago hatches out between midnight and 4 a.m., when the atmospheric humidity is high. The eggs are laid in dark, damp places where organic matter is present as

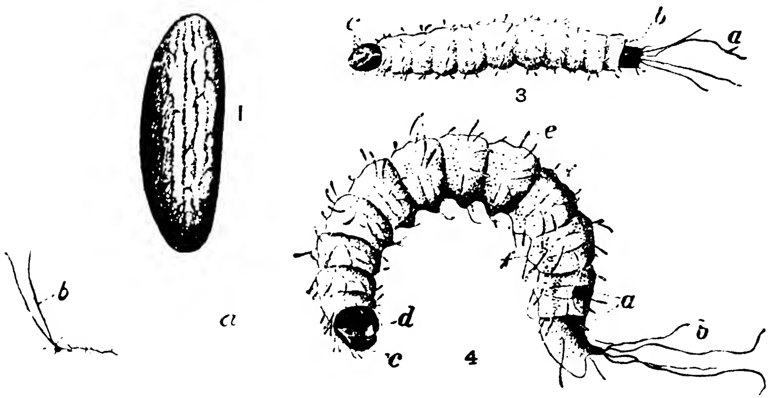


Fig. 322.—To illustrate life-history of *Phlebotomus papatasii*. (*After Whittingham, " Brit. Med. Journ."*)

1. Fertilized egg, seven days after oviposition. × 80.
2. First stage of larval life, two days old. *a*, Head with Y-shaped mark and egg-tooth; *b*, caudal bristles. × 40.
3. Third stage of larval life (dorsal view), thirteen days old. *a*, Caudal bristles; *b*, last segment; *c*, antennæ. × 20.
4. Fourth stage, twenty-two days old. *a*, Last segment; *b*, caudal bristles; *c*, mandibles; *d*, labial plate; *e*, body hairs; *f*, false legs. × 20.

food for the larvæ; usually this occurs in cracks or in masonry and at the base of walls and in stables, etc. Whittingham has shown that a very considerable amount of moisture is necessary for the successful rearing of these insects. In the situations indicated, it is possibly obtained from the water of condensation that collects there at night-time. Under artificial conditions Whittingham has succeeded in rearing the insects in cages containing sterilized nitrogenous matter at 80° F.

The breeding places of the various species vary in different parts of the world. In Peru the usual type of fence, composed of rubble and loose earth, provides breeding places for the local species; in Egypt they breed in damp cracks in the sandy soil, and in India *P. argentipes* in broken places in paved floors and in moist soil contaminated by the fæces of fowls and goats.

The adults are crepuscular and nocturnal in habit and are most active on warm, still nights. Sunlight repels them, but artificial light, especially if not too bright, appears to attract them. Their flight is feeble and short,

and when enclosed in a mosquito-net or on the bedclothes, they appear to hop or glide for short distances.

For the classification of these insects, entomologists have relied upon slender differences afforded by the venation of the wings, the segmentation of the palpi, and the number and arrangement of the bristles or spines on the claspers. Larrousse recognized 6 species in Europe, 11 in Asia, 4 in Java and the Philippines, 11 in Africa, and the same number in America.

The best-known species are *P. papatasii*, *P. perniciosus*, and *P. minutus* in Europe; *P. argentipes* and *P. perturbans* from India; *P. major* and *P. sergenti* from China; and *P. duboscqui* from Central Africa.

Repellents.—Various substances have been used on the skin with the idea of warding off these insects. Ordinary paraffin, if liberally applied to the skin, is effective. Waterston found that a substance called "*parquit*" is pleasant to use and, if well rubbed in, is efficient. Oil of citronella is also widely used for this purpose. (*See also* p. 134.)

In preserving specimens for identification great care must be exercised. They should be placed in a web-like layer of teased cotton-wool, but must not be *covered*, as even slight pressure damages their appendages.

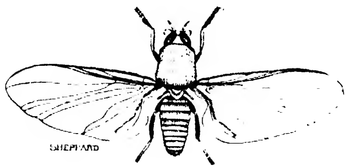


Fig. 323.—*Simulium damnosum*. × 10.

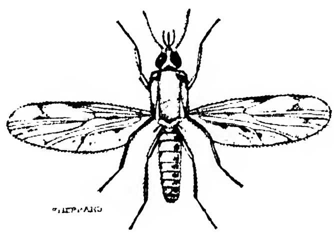


Fig. 324.—*Culicoides*, ♀. × 20.

Simulium (Buffalo-Gnats)

These small flies are extremely voracious. Both sexes feed on mammalian blood, commonly attacking cattle and human beings in the vicinity of their breeding-places. *S. damnosum* has been proved to be the intermediary host of *Onchocerca volvulus* in Central Africa. (Fig. 323.)

The following species are common in various parts of the world: *S. reptans* in Europe; *S. indicum*, the "potû" or "pipsa" fly of India; *S. damnosum*, the "jinja" fly of Central Africa; *S. vittatum* of North and South America. Numerous species occur in the Upper Amazon, and *S. avidum*, *S. ochraceum*, and *S. mooseri* are vectors of onchocerciasis in Guatemala (*see* p. 786), and are known as "*mosquito negrito*" and "*mosquito alazan*," respectively.

The eggs are laid in masses of 300–500 each, in water. They are triangular in shape, yellowish when fresh, but becoming black at a later stage. The larvæ emerge in two or three weeks, and immediately attach themselves to stones; they are cylindrical in shape, with a posterior swollen extremity. The pupa is attached to aquatic vegetation, and is encased in a cocoon open at the top, from which emerge a pair of branching gills. The larvæ of simulium are found only in flowing water, which seems essential to their normal development.

Family Chironomidæ

These are small, delicate flies, generally known as midges. The antennæ are plumose in the male and pilose in the female, in contradistinction to the almost bare antennæ of the Simuliidæ. They are a large family, comprising over 1,000 species; the most important genera from a medical point of view are *Culicoides* (Fig. 324) and *Leptoconops*, which in many parts of the world bite man viciously.

C. austeni and *C. grahami* have been found by Dyce Sharp to be the intermediary host of the filaria, *Acanthocheilonema perstans*. This insect is not only a night-biter, but will bite only in the dark and not at all by moonlight; it prefers dark skins. *Culicoides furens* transmits *Mansonella ozzardi* in the West Indies.

Life-history.—The eggs, which are very small and oval, are laid on algæ in shallow water. On hatching, the larvæ wriggle in the mud at the bottom of the pond. Usually they are red in colour, and are known as "bloodworms." They are provided with four pairs of gills. The pupa is furnished with no exterior casing, so that the wings and legs are fused to the thorax.

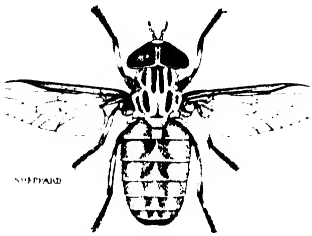


Fig. 325.—*Tabanus ustus*, ♂. Nat. size. (*Partly after Austen; by permission of Trustees of Brit. Mus.*)

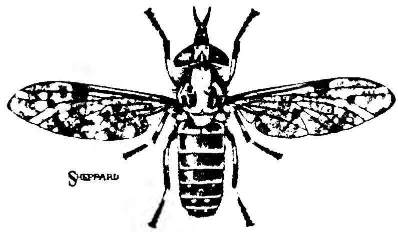


Fig. 326.—*Hæmatopota*, ♀. × 2½. (*Partly after Austen; by permission of Trustees of Brit. Mus.*)

Two long respiratory trumpets are present, and the adult emerges after three days.

BLOOD-SUCKING FLIES

In these flies the antennæ usually consist of three dissimilar segments, of which the third is elongated in many cases. The venation of the wings is complex; the second longitudinal vein is not forked. This section embraces the large family of Tabanidæ or "gadflies" (Fig. 325), *Hæmatopota* (Fig. 326) and the genera *Pangonia* and *Chrysops* (Figs. 327, 328).

The males of the genus *Chrysops* suck the nectar of flowers, while the females are extremely voracious, sucking the blood of men and animals.

The eggs, which are black in colour, are laid in masses of 250 each, on leaves of plants near water, where the larvæ are aquatic in their early stages, but later live in moist earth in proximity to water.

Chrysops discalis (Wilkeston, 1880) is a very common species in Central America, and is the transmitter (epidemiological and experimental) of tularæmia (p. 302).

Chrysops dimidiata (v.d.Wulp.) (Fig. 328), is a West African species common at certain times of the year in Nigeria and the Cameroons, and has been proved to be the intermediary host of *Loa loa* (p. 960). In this species the

face and palpi are yellow; the scutum is black with yellow stripes; the abdomen is yellow with dusky-brown tip; the legs are yellow with dark tibiæ and tarsi; the distal half of the wings is smoky.

Chrysops silacea (Austen), is also common in West Africa, and acts as an intermediary for *Loa loa*. It differs from the former species in having the abdomen red, or of a bright-orange colour, and the legs of the same colour with dark-brown tarsi.

Life-history.—The larvæ are about 10 mm. in length, and have a smooth skin; the 5th–11th segments on their ventral surface are provided with organs of locomotion which enable them to crawl about on aquatic vegetation. The pupa, which is brownish-yellow in colour, measures about 15 mm. in length. The anterior end is provided with four round projections.

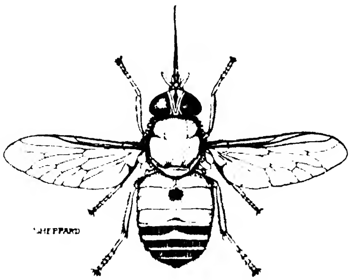


Fig. 327.—*Pangonia rüppellii*, ♀. × 1½. (*Partly after Austen; by permission of Trustees of Brit. Mus.*)

Fig. 328.—*Chrysops dimidiata* (v.d. Wulp.), ♀. × 2½.

Glossina (Wiedemann, 1830) (Tsetse Flies)

The species forming the genus *Glossina*, or tsetse flies, are sombre-coloured, narrow-bodied insects from about 6 or 8 to 13·5 mm. long, with a thick proboscis (*i.e.* proboscis enclosed by the palpi) projecting horizontally in front of the head. Their wings are large, of a brownish hue, and present a venation (Plate V, facing p. 160) which, though quite distinctive, somewhat resembles that of the warbleflies (*Hypoderma*). The most striking peculiarity in the wing is the course of the *fourth* longitudinal vein, which about the middle of the wing bends abruptly upwards to meet the short and very oblique anterior transverse vein; here describing a right angle, it runs obliquely downwards to meet the posterior transverse vein, and then turns upwards to reach the margin of the wing well in front of the apex.

When a tsetse is at rest its wings overlap on the back, closing one over the other like the blades of a pair of scissors (Fig. 329). This resting attitude of the wings, besides giving the fly a peculiarly elongated appearance, renders it readily distinguishable from other blood-sucking Diptera with which it might be confounded, *e.g.* the stable-fly (*Stomoxys*) and the cleg (*Hæmatopota*). *Stomoxys* (Fig. 332) is smaller in size, has short palpi not protecting the proboscis, and its wings diverge at an angle when resting. *Hæmatopota* (Fig. 326) presents prominent antennæ, and its wings are tectiform when closed, *i.e.* they meet together at the base like the roof of a house and diverge slightly at the tips.

In some species of *Glossina* the abdomen is crossed by sharply defined dark-brown bands, interrupted at the middle line. In the males, beneath the end of the abdomen the external genitalia form a conspicuous knob-like protuberance which renders the sexes easily distinguishable.

In this genus the palpi are long, deeply grooved on their inner sides, and closely applied to the proboscis, which they almost entirely conceal when it is not in use, the only uncovered portion being a peculiar large bulb-like expansion at the base. The proboscis consists of three parts (Fig. 330), *labrum*, *hypopharynx*, and *labium*.

The genus *Glossina* belongs to the subfamily STOMOXYDINÆ, of the family MUSCIDAE. The nearest related genera are *Stomoxys*, *Hæmatobia* (*Lyperosia auctt.*) and *Lyperosiops* (*Hæmatobia auctt.*); but on account of the limitation of existing species to the Ethiopian region, their peculiar structural features (bulb at the base of proboscis, remarkable male genitalia, characteristic venation of wings) and aberrant mode of reproduction, *Glossina* presents a marked individuality.[1]

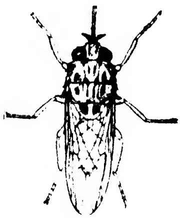


Fig. 329.
Tsetse fly at rest.
× about 1½.

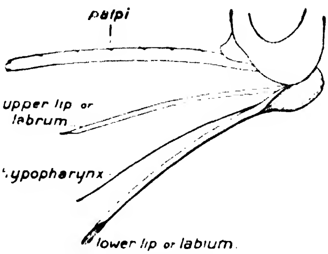


Fig. 330.
Mouth-parts of *Glossina*.

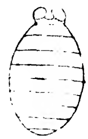


Fig. 331.
Pupa stage of *Glossina*.
× 2½.

The genus at present comprises twenty species, though this number is not necessarily final, since new species are discovered from time to time. Austen arranged the genus into four groups (*see* Table facing p. 1002).

Distribution.—Tsetse flies are confined to Africa and the south-western corner of Arabia. Some species, such as *G. fusca* and *G. morsitans*, have a very wide range throughout the greater part of intertropical Africa. *G. palpalis* is also widely distributed—from the Senegal to Angola on the west, and throughout the Lualaba-Congo system to the Victoria Nyanza, Tanganyika, and the Upper Nile at least as far north as Mvolo in the Sudan. The range of *G. austeni*, an East African species, extends from Jubaland to Zululand. *G. morsitans* ranges southwards to Bechuanaland, Southern Rhodesia and North-Eastern Transvaal, and northwards to Senegambia. Southern Kordofan, and Southern Abyssinia. *G. swynnertoni* a species described in 1923 and concerned in the dissemination of an outbreak of sleeping sickness, was thought to be confined to the Mwanza Province,

[1] Prof. Newstead in 1911 introduced a classification of species of *Glossina* based on a study of the male genitalia, which in this genus are characteristic. If macerated in potash the hypopygium can be turned backwards so as to display various complicated structures, namely the superior claspers, the editum, the inferior claspers, the harpes, the juxta or penis sheath, the median process, and the connecting membrane. All these vary in shape in different groups; the median process and connecting membrane are found only in some of them.

Tanganyika Territory (see p. 164), but has recently been found within the southern boundary of Kenya. *G. longipalpis* ranges through West Africa as far north-west as Senegal and south-east to the Katanga district of the Belgian Congo. *G. pallidipes* is found throughout East Africa from Zululand to the northern boundary of Kenya, while westward its range extends to the Katanga district of the Belgian Congo. Other species appear to be more restricted. *G. longipennis* is found in Somaliland and adjacent regions; *G. tachinoides* has a wide range in West Africa, and is said also to occur in Southern Arabia; *G. pallicera* ranges from Sierra Leone to the Belgian Congo; *G. newsteadi*, described in 1929, is only known to occur in the Lower Lomami region of Belgian Congo; *G. fusca* is found from Sierra Leone to Uganda; *G. brevipalpis* is common in South-Central and East Africa; *G. caliginea* is found in Southern Nigeria. Knowledge of the topographical distribution of these fles is an important matter. The species of *Glossina* are never found on mountains; they are seldom seen above 3,000 feet; they are absent from extensive plains or other open places; and are rarely met with in close cultivation. Cover, in the nature of bush, trees, or forest, is essential, and the species of the *G. palpalis* group are usually restricted to the neighbourhood of water, being found along the banks of rivers, brooks, and springs, round the coasts of lakes, and on slow rivers and lacustrine islands. They do not as a rule frequent a sudd-covered or sedgy-banked river or lake-shore or sedgy swamp, unless continuous with a belt of trees. The members of the *G. morsitans* group, however, as well as certain other species such as *G. brevipalpis*, are far from being confined to the immediate vicinity of water. The tracts infested by tsetse flies vary greatly in disposition and extent, according to the species concerned and the local or seasonal conditions. Thus, a so-called "fly belt" or "fly area" may be represented in one case by a narrow border of forest, but a few yards in width, along the edge of a stream; in another by a patch of "orchard bush"; or, yet again, as sometimes in the case of *G. morsitans* or *G. brevipalpis*, by a wide expanse of bush-covered or wooded country extending for many miles. It frequently happens that "fly belts" undergo enlargement during the rains and a corresponding shrinkage during the dry season, the flies extending their area of occupation in the period of maximum cover, and withdrawing again to the shelter of thicker patches of bush, or true forest, when bush fires or the withering of foliage threaten their exposure to the fierce heat of the sun.

Reproduction.—The species of *Glossina* do not lay eggs as do the majority of the Diptera, but, as in the case of forest-flies (Hippoboscidæ), the eggs hatch, and the larvæ feed, develop, and moult within the body of the parent, so that when extruded they are practically ready to pupate. In fact, the extruded larva becomes a pupa (Fig. 331) within an hour or two, the larval skin becoming a dark, rigid puparium. When extruded, the fully-grown larva is nearly asl arge as the abdomen of the mother; it is a yellowish ovoid body composed of thirteen segments and presenting two small hooks at the anterior pole, and two respiratory protuberances at the posterior end. which is black. A female tsetse fly deposits her larvæ singly, at intervals varying from about eight days to about three weeks, invariably choosing as a nursery a shaded spot where cover for the pupating larva is available in the form of loose, dry sand, humus, or vegetable debris. The necessary facilities in this respect are frequently afforded by the ground beneath fallen trees, where tsetse pupæ or empty pupa-cases are sometimes found in con-

siderable numbers. The perfect insect emerges from its pupa-case in about four to nine weeks.

Habits.—All tsetse flies feed on blood, certain species, such as *G. morsitans*, exhibiting great persistency and voracity in their attacks on man and animals. The blood-sucking habit, contrary to what is the case among horse-flies (Tabanidæ), Simuliidæ, and mosquitoes (Culicidæ), is not confined to the females, but is common to both sexes. *G. palpalis*, like *G. morsitans*, is active and ready to attack throughout the day, from an hour or so after sunrise onwards. As a general rule, *G. brevipalpis*, *G. fusca*, and *G. pallidipes*, all three of which haunt by preference the edges of paths, spend the greater part of the day resting motionless on tree-trunks. Though sometimes aggressive in the early morning, *G. brevipalpis* does not usually leave its hiding-place until late in the afternoon, when it remains on the wing until about half an hour after sunset. *G. fusca*, a more bloodthirsty species than *G. brevipalpis*, flies more silently, and, as a rule, bites only after dark. The period of activity of *G. pallidipes*, on the other hand, is usually in the afternoon, commencing and terminating before that of *G. brevipalpis*. While *Trypanosoma gambiense* is conveyed by *G. palpalis* and *G. tachinoides*, and *T. rhodesiense* by *G. morsitans* and *G. swynnertoni*, the rôle, if any, of the other species of *Glossina* in the dissemination of human trypanosomiasis is as yet unknown.

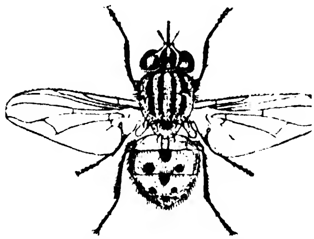


Fig. 332. *Stomoxys calcitrans*. × 3.

A synopsis of the characters of the four *Glossina* groups faces p. 1002.

Stomoxys calcitrans (Geoffroy, 1764) (Fig. 332)

This fly, which in many respects resembles the common house-fly, has a world-wide distribution. It can easily be distinguished from the latter during life by its stiff proboscis, as well as by the gentle curve of the fourth longitudinal vein. *Stomoxys* may enter houses and bite man, but it usually haunts the stables and feeds on cattle and horses; in the latter it transmits, probably mechanically, the trypanosome of "surra"—*T. evansi*.

The eggs, which resemble those of the house-fly, are deposited in horse-dung, and hatch in two or three days. The larvæ and pupæ greatly resemble those of the house-fly.

Other blood-sucking muscidæ which may attack man are *Hæmatobia stimulans* and *Lyperosia irritans*, the life-histories of which are in many ways similar to that of *Stomoxys*.

MUSCIDÆ THAT DO NOT SUCK BLOOD

Musca domestica (Linn., 1758)

The common house-fly (Fig. 333) is a cosmopolitan domestic species, and, on account of its insanitary habits, acts as a vector of pathogenic micro-organisms (especially the dysentery bacillus), *Entamœba histolytica* cysts, various other protozoa, and the eggs of helminths.

The insect is dark-grey in colour, with four parallel black stripes on the dorsum of the thorax, and measures about 8 mm. in length. The eggs are laid in masses in manure and other refuse, and hatch in twenty-four hours in hot weather. The larvæ are legless maggots bearing large stigmal plates on the abdomen.

The larva grows rapidly and, under the most favourable conditions of temperature and moisture, pupates in five days. The puparium has an elongate-barrel shape, and in the tropics

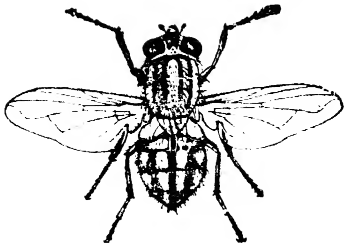


Fig. 333.—*Musca domestica*, ♀.

the pupal stage lasts about three days. The adult fly lives about a month. The larvæ are capable of traversing considerable thickness of soil in order to reach the surface—over 3 ft.

The best method of storing manure, if it is desired to keep it, is to ram it so tight that it ferments to such an extent as to destroy the maggots.

In tropical countries house-flies are in evidence all the year round, but in dry countries they die off, or the larvæ are killed, during the period of maximum heat and drought. In temperate countries these insects die off in the winter season, and are most numerous in early autumn. The larvæ survive by lying buried in decaying matter.

A nematode worm, *Habronema muscæ*, a stomach-worm of horses, is ingested by the larvæ of *M. domestica*, either in the egg or in the larval stage. The embryo of this worm continues its development in the fly, and the final larval stage is found in the proboscis of the adult insect.

FLESH-EATING FLIES

Wohlfahrtia magnifica (Schiner, 1862)

This species is 10–13 mm. in length, and of an ashy-grey colour. The head is slightly larger than the thorax, the vertex and frontal region are black, while the cheeks are satin-white, the palpi and antennæ black. The thorax is ashy-grey, with three longitudinal black stripes. The abdomen is light-grey, with three black spots adorning each segment. The legs are black.

This species is found in Russia and in Southern Europe, spreading to Egypt and Asia Minor; it frequents the open country, and breeds in living in preference to dead tissues.

In man the larvæ have been found in open wounds, in the nasal fossæ, palate, and eyes (*see* p. 850).

The larvæ of these various muscid flies can be identified by the shape of their posterior stigmata. (Fig. 334.)

Auchmeromyia luteola (Fabr., 1805)

A. luteola (Fig. 335) is widely distributed throughout tropical Africa. It ranges from Northern Nigeria to Natal, and has been found in the Sudan. It measures 10–12 mm. in length, and the body is rather stoutly built. The general colour is orange-buff, but numerous small black hairs give it a smoky appearance. The head is large, with eyes well separated in both sexes. The thorax shows two indistinct, dark, longitudinal stripes, which do not reach its posterior border. The abdomen differs in the two sexes, the second segment in the female being twice the length of the same in the male. The first segment has a narrow dark stripe on its posterior margin in both sexes; the second segment in the male is marked by a broader band, tapering forwards along the middle line to the base of the segment. In the female the dark band is so wide that it occupies almost the whole segment. The third segment is almost entirely black in both sexes. The fourth is dark at the base and lighter posteriorly. The legs are the same colour as the rest of the body. The first tarsal joint is jet-black, and stands out prominently against the large cream-white pulvillus. The wings are of a smoky-brown colour with conspicuous venation.

The larva (Fig. 336), known as the "Congo floor-maggot," is of a dirty-white colour and semi-translucent. It is in eleven segments, and grows to about 15 mm. in length. The central part of the ventral surface is flattened. At the posterior margin of each segment are three short limbs transversely arranged and provided with spines directed backwards. These enable the

maggot to move about caterpillar-like and fairly rapidly. Laterally the segments bear two or more irregular protuberances, each of which has a posteriorly directed spine and a small pit. The anterior segment is roughly conical, and bears the mouth, which is placed between two black hooks protruding from its apex and curved backwards towards the ventral surface of the body. Paired groups of minute teeth are placed around the two hooks

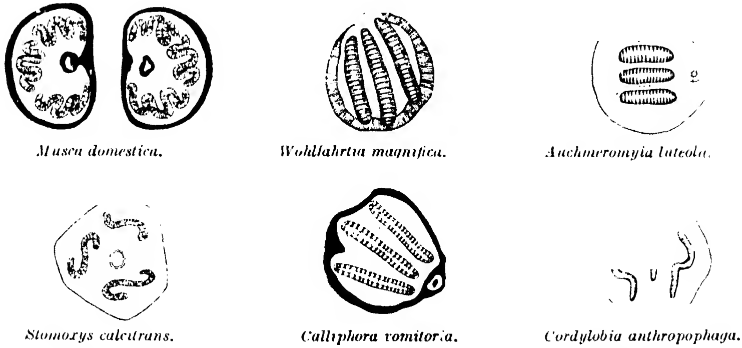


Fig. 334.—Stigmata of muscid larvæ, a means of rapid identification. Magnified.

so as to form a sort of cupping apparatus. The last segment is larger, depressed, and turned upwards at an angle of about 45° to the rest of the body ; two spiracles open on its dorsal surface surrounded by spines. The anus is placed in the anterior portion of its ventral surface, and behind

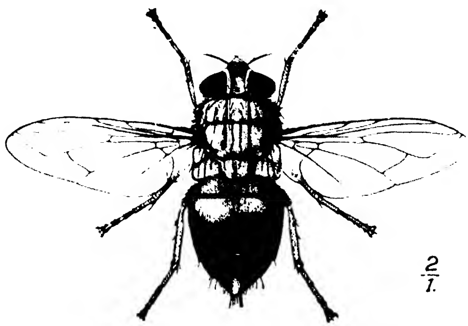


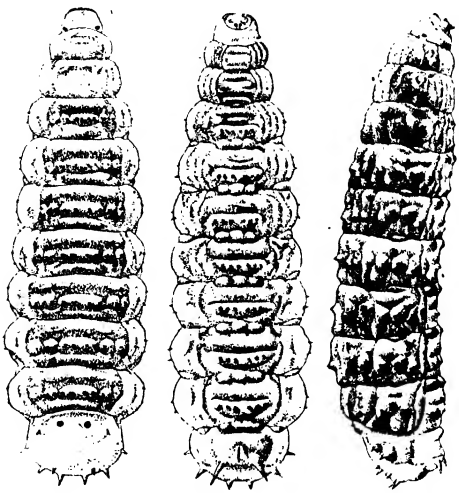
Fig. 335.—*Auchmeromyia luteola*, **female.**

it are two prominent spines. The alimentary canal commences with a short œsophagus which ends in a proventriculus. A remarkable dorsal diverticulum, corresponding to the food reservoir of the muscid larva, opens into the œsophagus near its anterior end. After the larva has fed, the diverticulum is a very conspicuous object, being seen through the semi-transparent body-wall as a bright-red area, extending, when full of blood, from the head

to about the fifth segment. The midgut is short; the hindgut is long, much coiled, and occupies the greater part of the body-cavity. The maggot has a thick integument, which enables it to withstand a good deal of pressure without injury.

The duration of the larval period has not been determined. When ready to pupate, the larva selects a suitable spot and lies dormant. The puparium is a dark reddish-brown oblong body, measuring 9–10·5 mm. in length by 4–5 mm. in breadth. The anterior end is roughly conical; the posterior is rounded. The pupa stage lasts from two to three weeks.

The fly is usually found sitting motionless among the thatch, beams, and cobwebs of the walls and roofs of native huts, but it is very difficult to see on account of its protective colouring, which corresponds exactly with



A B

Fig. 336.—**Larva of** *Auchmeromyia luteola*. × 5. (*After Brumpt.*)

A, Dorsal view; B, ventral view; C, lateral view.

the smoke-stained straw and rafters. It never bites, is usually silent, and deposits its eggs in the dust-filled cracks and crevices of the mud floors of the huts, particularly in spots where urine has been voided.

The larvæ are found especially under the mats on which the natives sleep, in the floor crevices, and in moist soft earth at a depth of 3 in. or more. They feed mainly or entirely at night, and they drop off at once if the limb on which they are feeding is moved. Those who sleep on beds or raised platforms are not attacked, as a rule, unless the bed be low, when the maggot may reach the occupant by crawling up the supports or the grass wall against which the bed is usually placed.

The larva of *A. luteola* may be recognized by the characteristic shape of the stigmata or openings of the respiratory tubes at the posterior extremity. (Fig. 334.)

COCHLIOMYIA MACELLARIA (Fabr., 1794) (Fig. 337)

THE SCREW-WORM

This insect is common throughout America. It is 9–10 mm. long; it lays a mass of 300–400 eggs on the surface of wounds, and in the ears and nasal fossæ. From these eggs the larvæ are hatched in a few hours. The

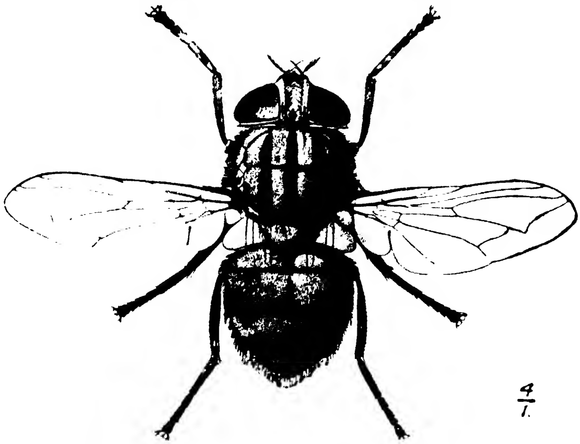


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Fig. 337.—*Cochliomyia macellaria*, female.

larvæ (Fig. 338) are white, about ¾ in. in length, and formed of twelve segments carrying circles of minute spirally arranged spines which give the creature a screw-like appearance. The larvæ burrow into the tissues, destroying cartilage and even bone; should the ear or nasal fossæ be attacked, the brain may be penetrated and death ensue.

Fig. 338.—*Cochliomyia macellaria*, larva × 5.

CHRYSOMYIA BEZZIANA (Villeneuve, 1914)

This species is found in India and in Cochin-China. It is 8 mm. in length by 13 mm. in breadth. In colour it is metallic blue; the thorax is bright green shading into blue, especially in the posterior half; the scutellum is blue.

In the *male* the eyes are reddish-brown and closely approximated; the cheeks are orange and covered with light silky hairs. The antennæ are deep orange. The abdomen is deep blue with green reflections, and the legs are black in colour. In the *female* the eyes are widely separated; the frontal stripe is broad, dark grey, and fringed with bristles. The *larva* is 12 mm. in length, yellowish-white in colour, with slightly pigmented extremities. The meso- and meta-thorax are encircled with a girdle of four rows of stout recurved spines. The posterior spiracles on the seventh segment are deeply placed in a horizontal slit, the anterior lip of which is well developed and provided with a pair of fleshy tubercles at each side of the middle line. The *puparium* is shorter than the larva, and of a deep mahogany colour. The *eggs* are laid in diseased tissues, and hatch in twenty-eight hours.

The larvæ cause great destruction of tissues, as in the preceding species.

CORDYLOBIA ANTHROPOPHAGA (Grünberg, 1903) (Fig. 339)

TUMBU FLY; "VER DU CAYOR"

This species is widely distributed in Central Africa. It measures from 8·5 to 11·5 mm. in length. It is of a yellowish-grey colour, with black spots on the abdomen and with brown-coloured wings, and much resembles *Auchmeromyia luteola*, but the male *Cordylobia* is distinguished from the male of that species by the closely-set eyes. In the female *Cordylobia* the abdominal segments are of equal size, while in the female *Auchmeromyia* the second segment is of greater length than the others. The fly is usually inactive, but, when disturbed, flies with great rapidity (Blacklock and Thompson).

The eggs are laid on soil, and the larvæ (Fig. 340) on emerging are very active; they are white in colour, are visible to the eye, and wander about till they find a suitable host (dog, man, or rat). In its early stages the larva is provided with adaptive structures, such as a cephalopharyngeal skeleton

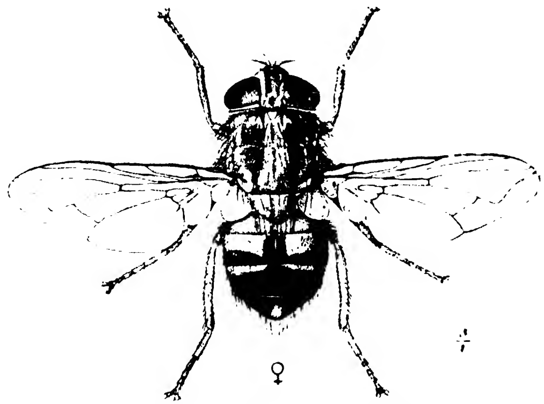


Fig. 339.—*Cordylobia anthropophaga.*

and cuticular spines, which assist it to penetrate the skin. There are three moults or instars. Development takes place in the subcutaneous tissues, and is complete in twelve days. The larva emerges from the swelling, which may be situated on forearm, scrotum, or other parts of the body, and, falling to the ground, pupates in thirty-six hours. The pupa has a characteristic shape with a square, truncated extremity. Pupa-cases are found in rat-burrows. The adult hatches in 10–20 days, according to the mean temperature of the locality in which it occurs.

Blacklock and Gordon have proved that in the case of the tumbu fly a remarkable example of metazoan immunity takes place. By placing Cordylobia larvæ of the first instar upon guinea-pigs, at the *first* experimental infection 49 per cent. survived to the sixth day; whereas only 7 per cent. survived this period in all subsequent applications. Local guinea-pigs are much less susceptible to first infection than those imported from England. All this evidences a great degree of immunity acquired by previous infection; it is not a general, but a local immunity parallel to that observed by Besredka in bacterial infection. No antibodies are present in the serum of immunized

animals. The immunity is at first localized in that particular area of the skin where it was acquired; it persists for at least three months and spreads from that area. Larvæ penetrating an immune area die within forty hours

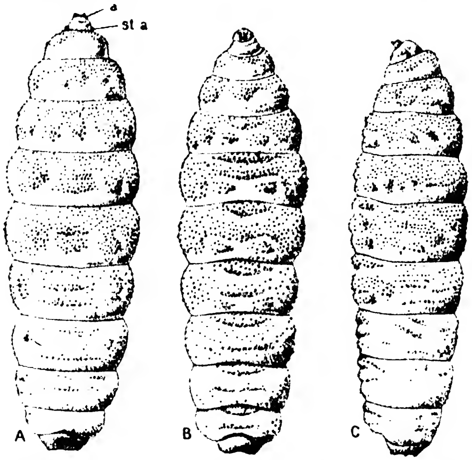


Fig. 340.—Adult larva of *Cordylobia anthropophaga.* × 5. (*After Brumpt.*)

A, Dorsal view; B, ventral view; C, lateral view.
a, Antennæ; *st.a.*, anterior spiracle.

while in the superficial non-vascular layers of the skin. Immune skin grafted on a non-immune animal retains and imparts its immunity; conversely a skin-graft from a normal animal acquires immunity when planted on an

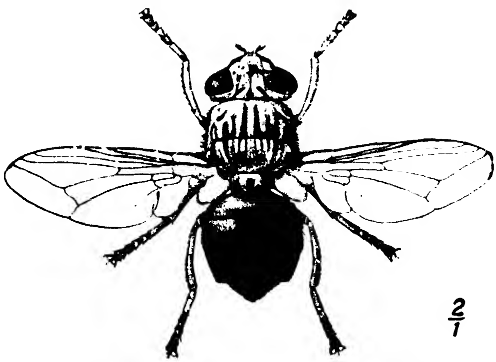


Fig. 341.—*Dermatobia cyaniventris,* **female.**

immune area. Metazoan infection is not invariably accompanied by an increase in the eosinophile cells.

BOT FLIES (*Œstridæ*)

Non-bloodsucking flies, with primitive mouth-parts, and parasitic in animals and man during the larval stages.

Dermatobia cyaniventris (Macquart, 1843) (Fig. 341) "Ver macaque"

This species is widely distributed throughout South America.

The larva occurs in the most diverse animals. It is found commonly in cattle, pigs, and dogs, but it occurs in the agouti, in the jaguar, in various monkeys, and in birds. It is rare in the mule, and writers have commented

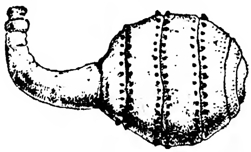


Fig. 342. — *Dermatobia cyaniventris* larva: early stage. (*Blanchard*).

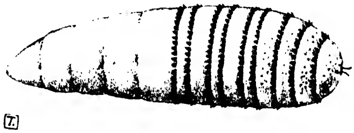


Fig. 343. — *Dermatobia cyaniventris* larva: later stage. (*After Brauer.*)

upon its absence from the horse. In man it has been reported from various regions of the body, namely, head, arm, back, abdomen, scrotum, buttock, thigh, axilla. Its presence is accompanied by excruciating pains, especially at those times when the larva is moving.

At an early stage the larva has the appearance represented by Fig. 342; at a later stage that represented by Fig. 343. The former stage is known

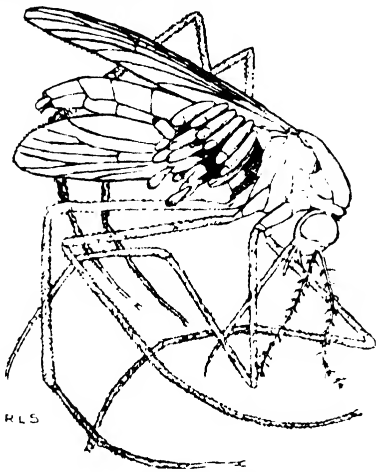


Fig. 344.—*Janthinosoma lutzi*, carrying eggs of *D. cyaniventris*. (*By courtesy of Tropical Diseases Bureau.*)

as *ver macaque*; the latter, much the larger, as *torce* or *berne*. At one time the larval stage of the same insect was erroneously supposed to belong to a different species.

Light has been thrown on the way this myiasis is acquired. On attaining maturity *D. cyaniventris* lays its eggs on damp leaves in damp places, the haunts of a species of mosquito, *Janthinosoma lutzi* (Fig. 344). More recently

Pinto and da Fonseca have shown that other species of insects can take on this function, such as *Sarcophaga terminalis, Musca domestica, Stomoxys calcitrans*, a tick, *Amblyomma cajennense*, and other mosquitoes: *Psorophora posticata, P. tovari*, and *Gœldia longipes*.

The packets of eggs are enclosed in a cement which, on becoming softened by moisture, adheres to the insect's thorax, and the eggs are thus conveyed to man or other vertebrates when it next commences to feed.

When hatched out, the larvæ penetrate the skin and produce an inflamed swelling about the aperture of entrance, from which a sero-purulent fluid, containing the black fæces of the larvæ, exudes.

Rhinœstrus purpureus (Brauer)

An important species of "head maggot" attacking horses in Russia, and in Egypt also. Its habits are similar to those of the common "bot-fly" *Œstrus ovis*. Like other species of related genera, it may attack man either in the eye or nose (*see* p. 850).

LICE

Lice are small, flattened, thin-skinned insects without wings, with mouth-parts adapted for sucking, and an indistinctly segmented thorax. Metamorphosis is incomplete. The number of abdominal segments ranges from six to nine, the last of which is bilobed. The abdomen of the male ends bluntly and bears a spine-like penis; the spiracles are very prominently situated on the sides of the abdominal segments. The eggs, or nits, adhere to the hairs of the host, and the newly-hatched young are small editions of their parents. The species which is parasitic on man is known as *Pediculus humanus*, of which there are two varieties, the head-louse, "*P. capitis*," and the body-louse, "*P. corporis*" (some regard them, indeed, as forming but one species). (Fig. 345.) The third species is *Phthirus pubis*, the "crab-louse"[1] (Fig. 346), which lives in the genital and inguinal regions. It is distinguished from other lice by its broad, flat body and by a line of three spiracles situated on each side of the second abdominal segment. The abdomen, of six segments, is festooned. The first pair of legs are more slender than the other two; the second and third have massive talon-like claws, the thumbs of the tibiæ being prominent. The phthirus, when adult, clings to two approximated hairs, generally about 2 mm. apart, the span between the hind-legs being about that distance. The young crab-louse passes through three moults before attaining maturity. The life-cycle is complete in twenty-seven days. When removed from man the crab-louse dies in forty-two hours. Infection with this louse occurs most frequently during coitus.

In *P. humanus capitis* and *corporis* the life-history is similar. The eggs hatch in from eight days at 32° C. to five weeks at a low temperature, and the young louse begins to suck blood at once. The immature louse moults three times before becoming mature; the final moult into the adult form takes place twelve days after hatching. Each adult female louse lays 8–12 eggs daily, while the total life-span of such an individual is from four to six weeks. These insects cannot live for any length of time upon discarded clothing, but under experimental conditions they live longer apart

[1] This species was originally placed in the genus *Pediculus* from which it was removed to *Phthirus* by Leach in 1815.

from the body at low temperatures; at 40° C. they survive twelve hours, and at 5° C. ten days.

Infection occurs through contact or close association with verminous persons. Spread is greatly favoured when men sleep huddled together.

Prophylaxis.—For the destruction of lice in clothing on a large scale, the most efficient method consists in the application of dry or moist heat. Both lice and nits are destroyed by a moderate degree of dry heat, 55° C. for five minutes, 65–70° C. for one minute. For practical purposes, clothes should be exposed to 70° C. for thirty minutes. Disinfection is best effected in hot-air huts. These measures may be supplemented by insecticide solutions, of which a 5-per-cent. crude carbolic solution containing soap is about the best; it may be used for leather and articles of clothing liable to be injured by heat. As a louse preventive, crude unoxidized naphthaline powder, as effective as N.C.I. and cheaper, may be dusted into the seams and renewed twice a week. Nearly all forms of treatment designed to kill lice upon the

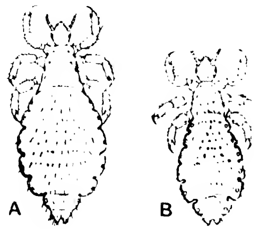


Fig. 345. — *Pediculus humanus.* × 5. (*After Bruce Cummings; by permission of Trustees of Brit. Mus.*)

A, *P. humanus*, ♀.
B, *P. humanus* var. *capitis*, ♀.

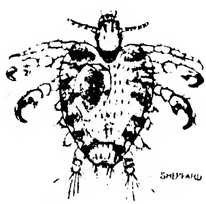


Fig. 346. — *Phthirus pubis*, ♀, **showing contained ovum.** × 12.

person aim at destroying the adult and immature insects, but do not destroy the nits or eggs. Chloroform water (5 : 1000) rubbed on the infected scalp or body, quickly stupefies all the living ones and renders their removal easy, but it leaves nits unaffected, and their removal from the hair is facilitated by vinegar or acetic acid (10-per-cent.). Mitigal (p. 970) is extremely useful for destroying the crab-louse (*Phthirus*).

Apart from their unpleasant habits, lice are of medical interest, since they act as intermediary hosts or transmitters in relapsing fever, typhus, trench fever, and possibly other diseases as well.

BUGS

Bugs have two pairs of wings; both may be membranous, or the front pair may have the basal half thickened to form a wing-sheath. The mouth-parts are adapted for sucking and piercing. The species parasitic on man are *Cimex lectularius*, the bed-bug of Europe, and *C. hemiptera* (*rotundatus*), the bug of warm countries, which can be distinguished by its more elongated, narrower abdomen, and by the greater dorsal convexity of the pronotum. (Figs. 347, 348.) In West Africa a species of another genus occurs, *Leptocimex boueti*, which also attacks man. The European

species was thought to carry the spirochæte of relapsing fever as the experiments of Rosenholz (1927) seem to show. During the day the insect hides in a crevice, and at night sallies forth to suck blood.

The eggs are white and oval, cohering together in clumps; each egg has a lid through which the larva emerges, resembling its parents in general appearance, but white in colour, and having no elytra or rudimentary wings.

The most effective method of destroying bed-bugs in a building is fumigation with sulphur or, better still, with hydrocyanic-acid gas; the latter, being dangerous, can only be carried out by some skilled person. For articles of furniture which cannot be subjected to boiling water, an emulsion of petroleum, made up with 3 parts of soap to 15 of hot water, to which, while still hot, 70–100 parts of oil are added, should be forced into all cracks and crevices with a brush. The latest method, and said to be the most effective, is by coal-tar naphtha. It is successful in killing off bugs and nymphs, but is far less toxic to the eggs. The concentration of naphtha which can be obtained at 60° F. is 0·20 per cent. and is lethal to all bugs exposed for twenty-four hours.

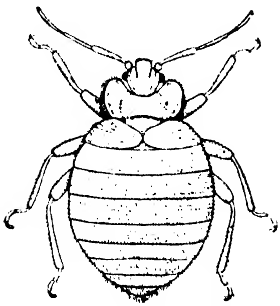


Fig. 347. — *Cimex lectularius.* × 7.

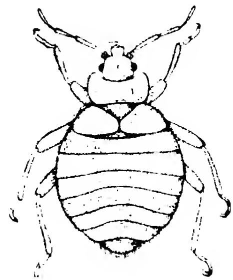


Fig. 348. — *Cimex hemiptera (rotundatus).* × 6.

Reduviid Bugs

This family includes a number of species which feed on human blood, inflicting painful bites. They are classified into four families, *Panstrongylus*, *Triatoma*, *Erathyrus*, and *Rhodnius*, the members of which are for the most part confined to America, from 41° N. to 41° S., while one (*T. rubrofasciata*) has a cosmopolitan distribution.

In nature they live entirely on wild animals, frequenting their nests or burrows, but certain species have become domesticated in modern human habitations. The adults of both sexes can fly for considerable distances, but the larvæ or nymphs are flightless, and can only bite human beings in their immediate vicinity. When engorged with blood after a feed, these insects void from the cloaca a white or dark-coloured fluid into the site of the bite, a habit which explains the manner in which *Trypanosoma cruzi* is transmitted (*see* p. 168). Two weeks after hatching, the females lay eggs which, in the case of *Panstrongylus*, *Triatoma* and *Erathyrus*, are deposited singly.

The larvæ, on emerging, engorge themselves with blood on four occasions, undergoing a moult after each; they then become nymphs, which, after

several feeds, moult for a fifth and final time before becoming adult. The whole cycle of evolution takes three or four months to complete.

The life-span is on an average one of three months, and when once infected with *T. cruzi* the insects remain so for the remainder of their lifetime.

PANSTRONGYLUS (Burmeister, 1835) AND TRIATOMA (Wolf, 1802)

(The genera *Panstrongylus* and *Triatoma* have been separated by C. Pinto (1931) on certain characteristics of the probosces and antennæ.

Synonym.—*Conorhinus* (Laporte, 1832).

This genus is distinguished by its smooth body and elongated or conical head.

P. Megistus (Burmeister, 1835)—Brazil—is a domestic species measuring 3 cm. in length. The body is black, with red stripes. (Fig. 349.) The insect has feeble powers of flight. The life-cycle takes a year to complete, and the adults can live about six months.

P. chagasi (Brumpt and F. Gomes, 1914)—Brazil—has a characteristic red band on the head, and lives in the burrows of *Cherodon rupestris* and those of armadillos.

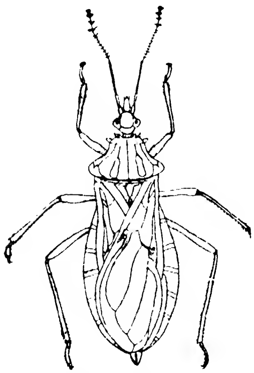


Fig. 349. — *Panstrongylus megistus*. Nat. size.

This species has been found infected with *Typanosoma cruzi* at a considerable distance from human habitations.

P. dimidiatus (Erichson, 1848)—Brazil, Venezuela, British Guiana, and San Salvador—is also naturally infected with *T. cruzi* and possibly conveys the human disease in San Salvador.

P geniculatus (Latreille, 1811)—Paraguay, Brazil, Peru, Venezuela, and French Guiana—is a sombre-coloured species, living normally in armadillo burrows; it transmits *T. cruzi* to these animals.

Triatoma infestans (Klug, 1834)—South America—is a domestic species and lives in cracks in the walls of houses or hen-roosts. It is found naturally infected with *T. cruzi* in Argentina.

T. protracta (Uhler, 1894)—the United States, from Utah to California—is known as the "kissing bug," and lives in the burrows of rodents. Under natural conditions it harbours a trypanosome, *T. neotomæ*.

T. rubrofasciata (de Geer, 1773), a cosmopolitan domestic species, can be infected experimentally with *T. cruzi*. It has been suspected, on rather imperfect evidence, of transmitting kala-azar in India.

T. sanguisuga (Lecomte, 1855)—United States—is a common domestic species which associates with bed-bugs. Under experimental conditions it can be infected with *T. cruzi*.

T. sordida (Stal, 1859)—Brazil, Bolivia, and Paraguay—is a small domestic species met with near the banks of the large rivers; it has been found naturally infected with *T. cruzi*.

T. vitticeps (Stal, 1859)—Brazil—is the largest known of these insects, and is a rare species.

GENUS ERATYRUS (Stal)

Erathyrus cuspidatus (Stal, 1859)—Venezuela—is believed to be a rare species, occurs at an altitude of 4,600 feet, and appears to be naturally infected with *T. cruzi*.

GENUS RHODNIUS (Stal, 1850)

This genus is characterized by a narrow attenuated head and by elongated antennæ (Fig. 350).

Rhodnius prolixus (Stal, 1859)—Venezuela, Colombia, Guiana, Brazil, and San Salvador. This species has nocturnal habits, and feeds voraciously on human blood (Fig. 350). Normally it lives in the burrows of the armadillo and those of a rodent (*Cœlogenys subniger*).

The adult is capable of flying considerable distances; the larvæ and nymphs live in cracks in the walls and in the crevices of palm trees.

Under experimental conditions this species can transmit *T. cruzi*.

FLEAS

Fleas are small insects with a laterally compressed body. They are wingless, and their mouth-parts are adapted for piercing and sucking. Some suck blood indiscriminately, but the majority restrict themselves to one definite host and are active ectoparasites of mammals and birds. (Figs. 351, 352, 353.) In one family, *Tungidæ* (*Sarcopsyllidæ*), or "chiggers," the females eventually attach themselves to their host as fixed parasites, embedding themselves in the skin when pregnant. (Fig. 354.)

The female flea is larger than the male. The curved receptaculum seminis is a conspicuous object.

The *eggs* are dropped by the female casually, and hatch in three or four days in summer-time.

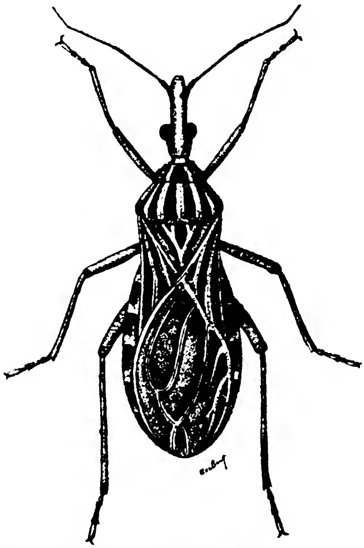


Fig. 350.—*Rhodnius prolixus*, **adult male.** × 2½. (*After Brumpt.*)

The *larva* lives in dust, is an active footless maggot of a whitish colour, is sparsely hairy, and lives on fæcal matter. (Fig. 355.) When full-grown it spins a cocoon and pupates. The duration of the pupal stage depends on the temperature. The pupæ are similar to the adult, and are encased in a cocoon. According to Barcroft, in the tropics fleas die out at a height of 14,000 feet.

Fleas act as mechanical carriers of disease, and also as intermediary hosts of parasites. The common dog-flea and the rat-flea harbour the cysticercus of certain tapeworms (*Dipylidium caninum* and *Hymenolepis diminuta*); but their most important rôle is as carriers of the plague bacillus from rats to man. In 1914 Rothschild pointed out that three species of *Xenopsylla*—*cheopis*, *astia*, and *braziliensis*—are ectoparasites of the rat in India. It is practically impossible to make out the distinguishing features of these three species unless the specimens are suitably prepared. With the aid of a hand-lens, the *females* can be recognized by the shape of the spermatheca after the

Fig. 351.—*Ctenocephalus canis*, **male.** × 16.
(*Major T. L. Bomford, I.M.S.*)

Fig. 352.—*Xenopsylla cheopis*, **male.** × 16.
(*Major T. L. Bomford, I.M.S.*)

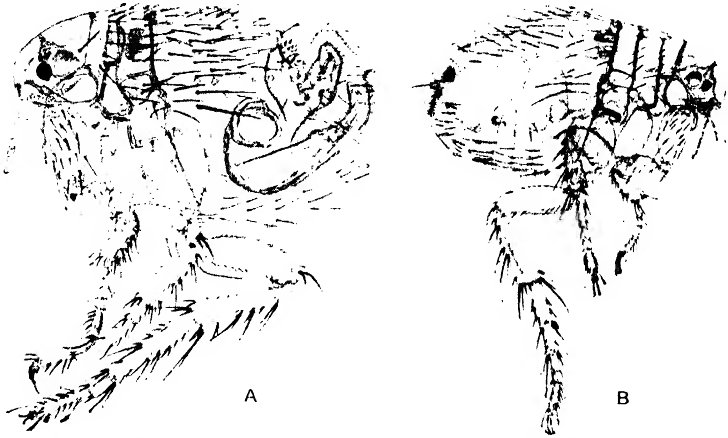


Fig. 353.—*Pulex irritans* A, **male,** × 25 ; B, **female,** × 14.
(*Major T. L. Bomford, I.M.S.*)

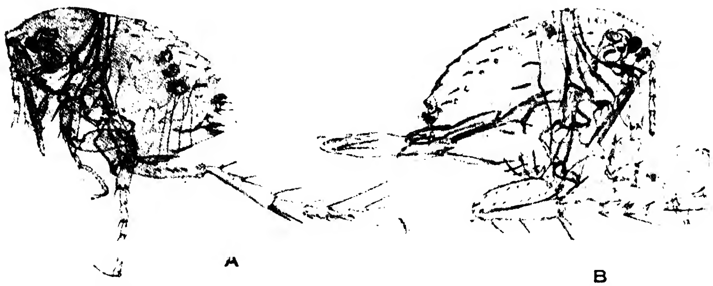


Fig. 354.—*Tunga penetrans* (*Dermatophytus penetrans, Sarcopsylla penetrans*) —**A, female : B, male.** × 38. (*Major T. L. Bomford, I.M.S.*)

soft parts have been dissolved by caustic potash, or rendered transparent by means of a clearing agent. For the certain identification of the *males*, a compound microscope is necessary, when it can be seen that the ninth sternite ends in a sharp point in *astia*, instead of a flattened projection, as in *cheopis*. The shape of the claspers differs in *astia* ; they are more elongated. These differential characters can only be relied upon in the case of fleas from the Indian area, because in that country only these three species exist.

After a short preliminary treatment with caustic potash, the fleas are treated with alcohol and xylol and placed overnight in a thin solution of balsam in xylol. Slides are prepared by coating the specimens with a thin layer of balsam and allowing them to dry overnight in the incubator. The fleas themselves are mounted and orientated on the slide ; the insects can then be individually examined under the microscope in rows of five each.

The presence of fleas in houses is chiefly due to want of cleanliness, especially the accumulation of dust, the proximity to hen-runs or stables, and free access of flea-carriers—cats, dogs, rats, and mice.

Prophylaxis.—To rid cats and dogs of these insects they should be washed with carbolic soap or a strong lather of "vermijelli." Cats that object to water may be powdered with naphthaline or dusted with pyrethrum. The floors of the house should be washed with a solution of naphthaline or benzene.

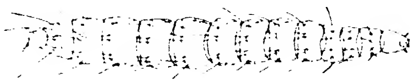


Fig. 355.—Larva of *Xenopsylla cheopis*. Magnified.
(*After Bacot and Ridgway, "Parasitology."*)

An emulsion of petroleum which will kill fleas when diluted with water, 1 : 20 or more, may be made from soft soap and ordinary petroleum, 3 parts of soap being melted by heat in 15 of water, and 70–100 parts of oil added while still hot, with much shaking and stirring. The final mixture should be white and creamy.

The irritation of flea-bites may be allayed by the application of 1 : 20 carbolic, or the following ointment:

	Acid. carbol. .	gr.x	(0·648 grm.)
	Menthol .	gr.v	(0·324 grm.)
	Zinc oxide .	ʒi	(3·89 grm.)
	Adipis prep. ad	℥i	(31·1 grm.)
or	Hydrarg. ammon. .	gr.x	(0·648 grm.)
	Liq. pic. carbon. .	ʒi	(3·55 grm.)
	Ung. paraff. (B.P.) ad	℥i	(31·1 grm.)

Xenopsylla astia (Rothschild, 1911)

In the *male* the antepygidial bristle is similar to that of *X. cheopis*, from which it is easily differentiated by the shape of the ninth sternite, which, instead of being club-shaped has the appearance of a ribbon, due to the chitinization of the ventral margin. The outer flap of the organs of copulation is narrower than in *X. cheopis*, and bears fewer bristles.

The "tail" of the receptaculum is so strongly widened near the constriction that it is much wider than the "head." The eighth segment has more than 30 bristles on its outer surface. (Fig. 356, 1.)

XENOPSYLLA BRAZILIENSIS (Baker, 1904)

In the *male* the long dorsal bristle on the seventh abdominal segment in front of the pygidium is placed on a long pedestal. In the *female* the " head " of the receptaculum seminis is very much wider than the " tail." (Fig. 356, 2.)

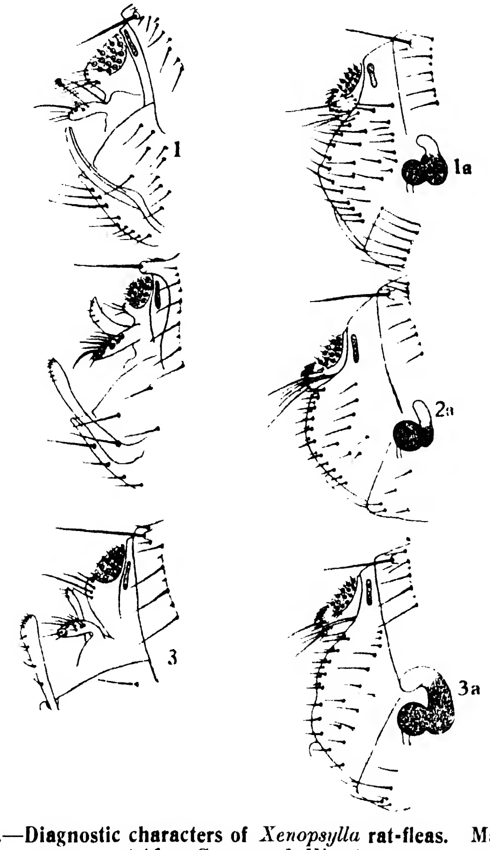


Fig. 356.—Diagnostic characters of *Xenopsylla* **rat-fleas.** Magnified. (*After Cragg and Hirst.*)

1, *X. astia* ; pygidium of ♂ ; 1a, pygidium and spermatheca of ♀. 2, *X. braziliensis* ; pygidium of ♂ ; 2a, pygidium and spermatheca of ♀. 3, *X. cheopis* ; pygidium of ♂ ; 3a, pygidium and spermatheca of ♀. Note shape and size of spermatheca.

XENOPSYLLA CHEOPIS (Rothschild, 1903)

In the *male* the ante-pygidial bristle is situated on a short pedestal. The outer flap of the copulatory organs is sole-shaped : its upper edge is more curved than the lower, and bears 9 or 10 bristles on its outer surface, all of them thinner than in *X. braziliensis*, and drawn out into a long, thin point. The ninth sternite has the appearance of a club, the upper side of which is flattened.

In the *female* the " tail " of the receptaculum is much longer than in the preceding species and, near the constriction, is distinctly wider than the " head." (Fig. 356, 3.)

Section B—Laboratory Methods

I.—CLEANING SLIDES

NEW slides are suitable for making blood-films, directly the superficial grease is removed, by breathing on them and rubbing up with a clean handkerchief.

Slides which are dirty or have previously been used should be boiled in a soapy solution for about half an hour, then washed in several changes of water, dipped in methylated spirit, and finally polished with old linen.

Cover-slips and slides are apt to become frosted when kept long in the tropics ; in order to prevent this they should be kept in spirit.

II.—METHODS OF PREPARATION OF BLOOD-FILMS

THIN FILMS

Take on the end of a slide a droplet of blood, obtained by pricking the cleansed finger or ear-lobe[1] ; if possible, no pressure should be exerted, and care should be taken not to touch the skin. A second slide should be touched, about ¾ in. from the end, with the drop, and the blood allowed to run along the edge. The spreading slide should be pushed, at an angle of 45°, to the opposite end of the horizontal, leaving a thin and evenly-spread film which should be allowed to dry. (Fig. 357.) An angle of less than 45° makes a thinner, and one greater than this angle, a thicker film. (Fig. 358.)

A lancet-pointed hare-lip pin makes a very satisfactory instrument for pricking the finger. If such a pin be not handy, a good supply of blood can be obtained by means of a glass needle which is made by drawing out a Widal tube and knocking off the point an inch from the pointed end.

Films for making a differential count of cells should be prepared by pressing unevenly upon the slide, so as to obtain a wave-like film. By this means the leucocytes collect along the edges of the waves, enabling the enumeration to be done more rapidly.

THICK FILMS

Ross's thick film is made by allowing some six drops of blood to fall on a slide within an area 5–7 mm. in diameter, and spreading them into an even layer. After dehæmoglobinization with water, the resulting film is dried in air. The film should then be stained with Leishman's or Giemsa's stain, as detailed at p. 1023.

There is considerable difficulty in differentiating the younger forms of tertian and quartan from subtertian malaria parasites by this method, such details as Schüffner's dots being rendered invisible. It is, however, very useful for demonstrating parasites in scanty infections, especially in the case

[1] Blood from the ear is not so satisfactory as that obtained from the finger. *See* p. 1026.

of rings and gametocytes, and it is also useful for the demonstration of the spirochætes of relapsing fever and trypanosomes when these, as is often the case, are extremely scanty (*see* Plate IV, *1*, facing p. 68).

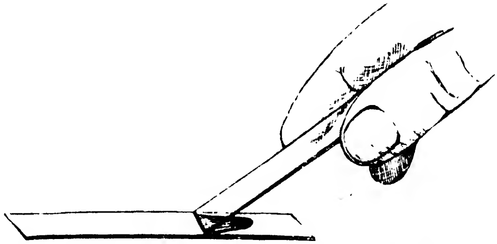


Fig. 357.—Method of spreading a blood-film.

Films for demonstration of filarial embryos.—An even larger-sized drop should be taken (20 c.mm.) and spread so as to occupy an area of ½ sq. in. on the slide. (Fig. 359.) For this purpose the finger should be pricked

Fig. 358.—Successful thin blood-film. (*Orig.*)

359.—Thick blood-film. (*Orig.*)

with a broad-pointed needle and the surface of the slide dabbed with four good-sized drops. The film is allowed to dry, protected from dust (especially cotton fibres, which may simulate microfilariæ), dehæmoglobinized, and

stained at the same time in a dilute watery solution of fuchsin (5 drops to 150 c.c. distilled water), then examined in a wet state under a low power of the microscope.

Preparations for the Study of Fresh Blood

A small drop of blood should be taken upon a clean slide, inverted, and allowed to come into contact with a clean cover-slip upon a filter-paper. If no pressure is used, the blood spreads out evenly, the corpuscles tending to congregate round the periphery while the centre remains clear. The preparation may then be ringed with vaseline, and the blood-cells or contained parasites studied in the living state under a $\frac{1}{12}$-in. lens. Should it be desired to study the action of living cells (vital staining), a vaseline ring or square of the size of a cover-slip is made upon a clean slide. Then a solution of 0·85-per-cent. NaCl with 1-per-cent. sodium citrate is tinted with methylene-azur, gentian-violet, or methyl-green, and taken up in a capillary pipette, together with an equal volume of blood. After mixing quickly on a slide, a small drop is placed in the centre of the vaseline ring and immediately covered with a cover-slip and pressed down.

III.—STAINING OF BLOOD-FILMS FOR PROTOZOA AND FOR THE DIFFERENTIAL COUNT OF CELLS

Leishman's method.—For this method *no preliminary fixation* is required.

Preparation of stain from the powder—0·15-per-cent. solution dissolved in methyl-alcohol (acetone-free). The powder is placed in a glass mortar, a quantity of methyl-alcohol added, and the powder ground down with a pestle until the alcohol is saturated. The fluid is then decanted off into a clean bottle and a further fraction of methyl-alcohol added to the residue in the mortar, which is again ground down until as much as possible is dissolved. This process is repeated until the whole of the powder is in solution, and sufficient methyl-alcohol is finally added to the stain to make up the required volume.

Method of staining.—1. Select the most suitable part of the blood-film and place a grease-pencil mark on each side, about 1 in. apart—a method which in staining large batches of films results in great economy. 2. Cover the selected part with stain by means of a pipette, and leave for a minute, taking care that it does not dry. 3. Dilute the stain about 1 in 4 with distilled water, *which must not be acid in reaction* (fresh rain-water may be used), and allow to act for a further 5 mins. (*See* Tribondeau's test, p. 1025.) 4. Wash off the stain with distilled water and leave a drop on *for a minute* to differentiate; place in a sloping position to drain.

For permanent preparations, Leishman-stained slides must *not* be mounted in Canada balsam, as they rapidly fade, unless it is neutral in reaction or dammar lac be used; they should be examined, unmounted, direct in cedar-wood oil, and the oil subsequently removed by means of xylol.

Giemsa's stain.—It is best to obtain the stain already prepared for use by Grübler. *The film must first be fixed* by placing in a mixture of equal parts of absolute alcohol and ether for 10–15 mins.

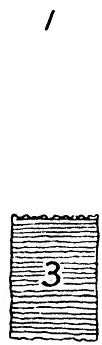
Method of staining.—1. The film should be covered with a 1 : 20 dilution of the stain (1 drop to 19 drops distilled water), which is allowed to act for

20–30 mins. 2. Wash off the stain with distilled water. Place the slide in a sloping position to drain, or dry with blotting-paper.

Hæmatoxylin and eosin.—For studying the finer structure of the leucocytes, and especially the nuclear changes, blood-films should be stained with hæmatoxylin and eosin.

After fixation in alcohol and ether for 10 mins. the film should be stained with Delafield's hæmatoxylin for 7 mins. The stain should be well flushed off the film with a good flow of tap-water, and it should be left in a running stream of the same for an equal period in order to "blue" thoroughly. While still wet it should be counterstained with a watery solution (5-per-cent.) of eosin for 30 secs., after which it should be thoroughly rinsed in tap-water for another 3 mins. in order to differentiate the eosin.

Method of staining the flagellated body in malaria.—A sheet of thick blotting-paper, having rows of oblong holes (1 in. by $\frac{2}{3}$ in.), is prepared; it is slightly but sufficiently moistened with water, and laid smoothly on a sheet of window-



A patient in whose blood the gametocyte form of the parasite abounds is selected. A clean microscope slide is breathed on once, and the droplet of gametocyte-containing blood immediately taken up by lightly touching it with the centre of the breathed-on surface of the slide. The blood is now rapidly and somewhat unevenly spread out with the needle so as to cover an area of about $\frac{3}{4}$ in. by $\frac{1}{2}$ in. The slide is immediately inverted over one of the blotting-paper cells and pressed down sufficiently to secure thorough apposition of the slip to the paper, without, at the same time, bringing the blood into contact either with the moistened paper forming the wall, or with the glass forming the floor of what is now a very perfect moist chamber. The remaining paper cells are rapidly covered with blood-charged slides prepared in the same way. Slides are removed and dried at intervals of from 5–20 mins. and are subsequently stained by Leishman's method.

Fig. 360.—To illustrate McKay's method of staining flagellated body.

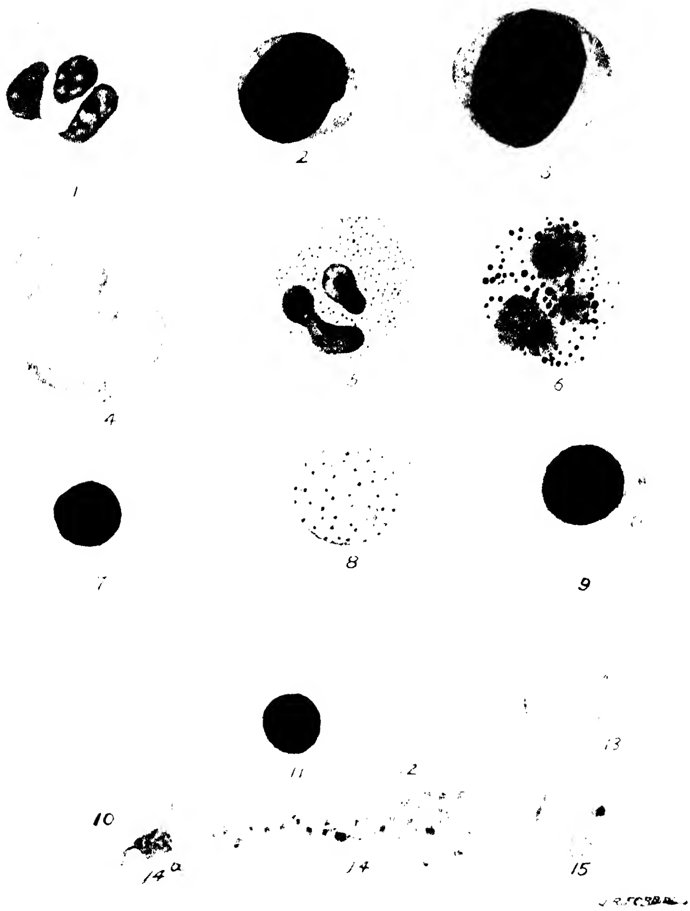
1, Slide bearing freshly-made blood-film; 2, pad of damp filter-paper; 3, size of opening showing blood-film and forming with the opposing slide an hermetically sealed damp chamber.

McKay's method.—This is an abbreviated but more effective method. A thin film of crescent-containing blood is made upon a thin slide (1 mm. in thickness, so as to be easily focused through a $\frac{1}{6}$-in. lens). The wet film should be breathed upon and then placed face downwards upon a second slide covered with a small piece of damp filter-paper, in the centre of which a small opening is cut. The two slides are bound together by means of elastic bands, thus forming a tightly sealed damp chamber. The exflagellation of the crescent can now be observed under the microscope, and immediately this occurs the film is dried and stained in the ordinary manner. (Fig. 360.)

Plate XXXII

NORMAL AND ABNORMAL BLOOD-CELLS.

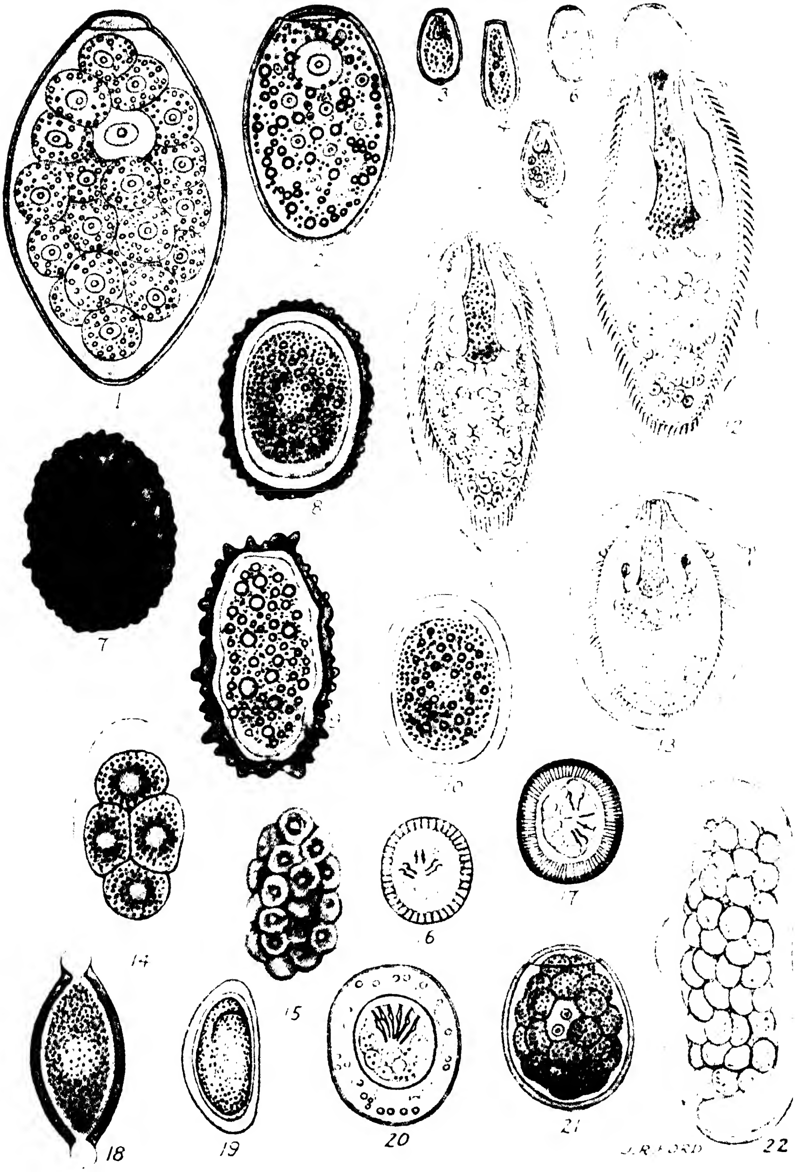
1.—Neutrophile polymorphonuclear leucocyte.
2.—Small lymphocyte.
3.—Large lymphocyte.
4.—Hyaline or large mononuclear leucocyte.
5.—Eosinophile leucocyte.
6.—Basophile leucocyte (" mast-cell ").
7.—Normoblast (nucleated red cell).
8.—Basophilic dots in red cell.
9.—Megaloblast.
10.—Megalocyte.
11.—Microblast.
12.—Microcyte showing poikilocytosis.
13.—Polychromatophilic degeneration of red cell.
14, 14*a*.—Various appearances of blood-platelets.
15.—Blood platelet superimposed upon a red cell.



NORMAL AND ABNORMAL BLOOD CELLS.

× 2 000 Leishman's stain

Plate XXXII



EGGS OF THE COMMONER HELMINTHS
FOUND IN MAN.

PLATE XXXIII

PLATE XXXIII

EGGS OF THE COMMONER HELMINTHS FOUND IN MAN. × 400.

1. —*Fasciolopsis buskii.*
2. —*Paragonimus ringeri.*
3. —*Heterophyes heterophyes.*
4. —*Opisthorchis felineus.*
5. —*Clonorchis sinensis.*
6. —*Loxotrema ovatum* (Yokogawa's fluke).
7. —*Ascaris lumbricoides* (external aspect).
8. — „ „
9. — „ „ (unfertilized egg).
10. — „ „ (decorticated egg).
11. —*Bilharzia hæmatobia.*
12. — „ *mansoni.*
13. — „ *japonica.*
14. —*Ancylostoma duodenale.*
15. —*Trichostrongylus colubriformis.*
16. —*Tænia solium.*
17. — „ *saginata.*
18. —*Trichuris trichiura.*
19. —*Enterobius vermicularis.*
20. —*Hymenolepis nana.*
21. —*Diphyllobothrium latum.*
22. —*Heterodera radicicola* (non-parasitic, ingested with vegetables).

Tribondeau's hæmatoxylin test for reaction of distilled water.—Two drops of a saturated alcoholic solution of hæmatoxylin should be added to a test-tube half-filled with the water under examination. If the water be neutral, the purple colour of hæmatoxylin will develop in 2–4 mins.; if alkaline, the colour develops immediately; if acid, it is delayed.

IV.—VARIETIES OF BLOOD-CELLS AND THEIR SIGNIFICANCE (Plate XXXII)

The average total leucocyte-count, as performed on a Thoma-Zeiss hæmocytometer, is 7,000 per c.mm. of blood. A rise to above 10,000 indicates a *leucocytosis*, a fall to below 5,000 a *leucopenia*. In making a differential leucocyte-count, at least 300 cells should be counted under the $\frac{1}{12}$-in. immersion lens, and by means of a movable stage the preparation should be moved from side to side, so as not to traverse the same field twice. In a "wave" preparation the edge of the thickened portions will be found to contain the majority of the leucocytes; a knowledge of this fact will save considerable search.

The neutrophile polymorphonuclear (or microphage).—Normal proportion, 60–70 per cent.; average, 67. By staining with Romanowsky stains, the neutrophil granules actually stain slightly acidophil. The variation in shape of the nuclei is due to a subdivision of the nucleus from one to four or even more lobes, and this affords some indication of the age of the cell. Thus a count of the percentage of these cells with different numbers of lobes has been used by Arneth, Schilling, and others as a basis of diagnosis and is known as the "Arneth index." A shift to the left is noted in liver abscess, pneumonia, relapsing fever, and in any septic process. Size when spherical, 12 μ.

The precursor of the polymorph cell is a bone-marrow cell, the *myelocyte*, the most mature individuals of which cell contain granules and mitochondria.

Eosinophile.—These cells are a little larger than the polymorphonuclear leucocyte—12–14 μ—and contain characteristically coarse eosinophile granules. Usually the nucleus has not as many lobes as the polymorphonuclear, two being the average number—the so-called "spectacle arrangement." Normal proportion, 2–4 per cent.; average 3 per cent. Eosinophiles are increased in all helminthic diseases—in ancylostome, dracunculus, and clonorchis infections, 5–10 per cent.; in filariasis and paragonimiasis, 10–20 per cent. (*L. loa* infections up to 60 per cent.); and in bilharziasis and trichinosis, 20–60 per cent. of the total leucocyte-count. In ascaris and diphyllobothrium infections there may be little or no increase.

Basophile.—Slightly smaller than the polymorphonuclear—10–12 μ in diameter. The nucleus is kidney-shaped or slightly lobulated. The cytoplasm contains purple large granules which often obscure the details of the nucleus. Usual proportion, 0·5 per cent.

Lymphocyte.—The lymphocyte is derived from the lymphatic tissue of lymph-glands throughout the body and other collections of lymphatic tissue. The *lymphoblast* contains an oval nucleus, poor in chromatin, with a recticular structure, coaser and more stippled than the myeloblast, and is found in acute lymphatic leukæmia. The normal proportion of lymphocytes is 19–30 per cent.; average, 23. The small lymphocyte is 5–8 μ in diameter, the large 12–15 μ; the latter is assumed to be the immature form. This

cell is increased after physiological digestion, in undulant fever, pellagra, typhoid and allied fevers, and relatively also in kala-azar.

Large hyaline, or mononuclear (monocyte-macrophage, including transitional).—Size, 16–22 μ. Normal proportion, 3–8 per cent. ; average, 6 per cent. This cell tends to be increased in protozoal diseases, trypanosomiasis, and malaria ; in the latter it often contains ingested hæmozoin. In making an estimate of the proportion of mononuclear cells in a film, not less than 300 leucocytes should be counted. Should the ear be selected for obtaining blood, it is important that no drop earlier than the third should be used, for it has been shown that the mononuclears tend to accumulate in the capillaries of the ear, if the local circulation is slow. It is now known that the large mononuclears are derived from the spleen and bone-marrow and are not related to the lymphocyte, therefore the " transitional cells " must be regarded as mature mononuclears. The cytoplasm contains fine reddish-blue granules.

The *monocyte* has to be distinguished from the *clasmocyte*. The former originates from the reticulum, the latter from the endothelium. They both have the same morphology, staining reactions, and nuclear structure, as shown by ordinary stains, but by vital staining, the clasmocytes take up trypan-blue freely, while monocytes do not.

A proportion of 15 per cent. or over of these cells may be considered a reliable aid to the diagnosis of malaria ; a proportion of 10 per cent. may occur in a normal person, and a percentage above this calls for further investigation. There is no increase of monocytes during the pyrexia of a malarial attack, but an increase may take place during the apyretic period.

Leucocytes in childhood.—The leucocytes are more numerous in the child than in the adult ; 12,000 per c.mm. is the average number throughout infancy. The percentage of lymphocytes is doubled, that of the neutrophiles is halved. The adult proportion, as given above, is reached about the tenth year.

Normal red cell (erythrocyte).—Size, 7·2–7·5 μ in diameter. Normal number, 5,000,000 per c.mm., or a little over. They are biconcave discs, and therefore considerably thinner in the centre than at the periphery. The erythrocytes are derived from reticulocytes in the bone-marrow. The cell membrane of the latter is sticky, so that the cells adhere to one another and to the capillary wall. In the process of becoming mature, the stickiness gradually diminishes. Abnormal red cells are known as ovalocytosis, and elongated forms as sickle-cells (p. 38). A total red count, computed from 64 squares on the Thoma-Zeiss hæmocytometer, of under 3,000,000 denotes a severe anæmia, and is usually accompanied by degenerative changes in the red cells—e.g., malaria, blackwater fever, sprue, ancylostomiasis and Oroya fever.

Distinctive forms of red cell—the *reticulocytes*—have been found to be young red cells formed from normoblasts by extrusion of the nucleus. Reticulocytes constitute a constant sign of blood-regeneration, and may be stained by cresyl-blue. They are larger and stain more lightly than mature red cells and their stroma contains a blue-staining reticulum. In normal blood these cells amount to 1 per cent., but during blood-regeneration they may reach 20 per cent. of the total number of erythrocytes.

Anisocytosis denotes variations in size of red cells ; it is found in various conditions of anæmia, especially of the pernicious type. **Poikilocytosis** denotes pear-shaped distortion of cells, giving the idea of fragmented

corpuscles, and are found in anæmic conditions. **Spherocytosis** denotes increase of thickness and is found in acholuric jaundice where the cells stain densely.

Megalocyte.—A red cell of abnormal size and shape, generally associated with **microcytes**—i.e., small red cells smaller than the normal 4 to 6·5 μ in diameter. Megalocytes are indicative of degenerative changes of the blood in the severe anæmias of blackwater fever, subtertian malaria, Oroya fever, sprue, and pernicious anæmia. (*See* pp. 36, 37.)

Nucleated red cell, or normoblast.—Present in very small numbers in normal blood, increased in severe plastic anæmias—e.g. malarial cachexia, blackwater fever, sprue, ancylostomiasis, kala-azar, and Oroya fever—and in severe helminthiasis. The nucleus is sometimes double or bilobed, and the protoplasm of the cell is usually polychromatophilic. Supravital staining shows a well-marked reticulum in the cytoplasm. These cells are generally present in considerable numbers in spleen punctures in kala-azar, severe malaria, visceral bilharziasis, pernicious anæmia, and splenic anæmia.

Polychromatic degeneration of red cells.—Present in subtertian malaria, blackwater fever, and severe anæmia. The term *polychromasia* denotes a degeneration of the red cell, the cytoplasm of which stains light blue; when severe it is generally accompanied by the formation of polychromatic, or basophilic, dots. It is now generally accepted that *polychromasia* and stippling are both manifestations of reticulation and that the polychromatic cells of a Leishman-stained film and the reticulocytes of a supravitally-stained film are identical and normal. Polychromasia is found in malaria, Oroya fever, pernicious anæmia, ancylostomiasis, and lead-poisoning.

Megaloblast.—An abnormal nucleated red cell found in severe anæmias of the pernicious type, including diphyllobothrium infections, and in size sometimes reaching twice that of a normal erythrocyte. The cytoplasm is non-granular and deeply basophilic, the nucleus large and pale, occupying more than half the cell body, which contains no hæmoglobin. Its presence in the blood generally indicates a regeneration from the blood-forming cells of the bone-marrow.

Blood-platelets.—Size about 3 μ in diameter, round, oval, or rod-shaped, according to the viewpoint, but variability in size is a feature of essential thrombocytopenia. When resting on red cells they may simulate malaria parasites, but there is always a clear zone due to pressure surrounding the platelet (Plate XXXII, Fig. 15). When drawn out in making the film they may simulate a trypanosome. They are generally found in masses or in strings, are coated with some adhesive substance, and cling to any stationary object. Their function is connected with the clotting of the blood.

Blood in the Tropics.—Investigations on the blood-picture of Europeans living under tropical conditions have been undertaken in Iraq and elsewhere, to discover any changes in the blood-picture from the generally-accepted normal. No striking differences are apparent. A marked deviation of the Arneth, or polymorph index to the left, similar to that reported in the indigenous natives, has been reported (*see* p. 16.).

V.—BIOCHEMICAL METHODS OF EXAMINATION OF URINE

1. In Malaria

(1) Examination of the urine for urobilin.—*Schlesinger's test* is used:—10 grm. of zinc acetate are added to 100 grm. of alcohol and shaken.

A portion of this suspension is mixed with an equal quantity of urine and filtered through a double filter. If much urobilin is present a definite green fluorescence appears. A very high content of urobilin can be recognized by adding a few drops of zinc chloride and ammonia to the urine, which produces the characteristic fluorescence.

(2) Examination of the urine for urobilinogen.—Fresh urine must be used, as urobilinogen changes to urobilin when the urine is left standing. The test is based on *Ehrlich's benzaldehyde reaction* :—2 grm. of dimethyl-para-aminobenzaldehyde are dissolved in 100 c.c. of 5-per-cent. hydrochloric acid ; 10 to 15 drops of this reagent added to 10 c.c. of normal urine produces, when warmed, a reddish coloration of varying intensity, since every urine contains traces of urobilinogen. In testing for the presence of an increase in the urobilinogen content, a cold test, in addition to the warm one, is made. In the warm solution the coloration occurs immediately, but only after a few minutes in the cold. If the urobilinogen content is not above normal there is no coloration in the cold solution within this short period.

(3) Tests for blood in the urine.—If blackwater fever is suspected the urine must be examined for blood as well as albumin.

(*a*) *Spectroscopic examination* is the simplest. After dilution, absorption lines characteristic of oxyhæmoglobin are seen in the yellow and green, between the Frauenhofer lines D and E. This test, however, is positive only if there is a rather high blood-content.

(*b*) *Boas's test.*—Boas's reagent is made as follows :—1 grm. of phenolphthalein is dissolved in a solution of 25 grm. of potassium hydroxide in 100 c.c. of water ; 10 grm. of powdered zinc are added and the mixture is boiled until the red colour is discharged. The hot liquid is filtered and a further small amount of powdered zinc added to prevent oxidation. For the test, 15 drops of Boas's reagent are mixed with 20 drops of 96-per-cent. alcohol and 5 drops of hydrogen peroxide in a test-tube, and the mixture is added slowly to the urine in a test-tube to form a separate layer. If blood is present, a red ring appears where the liquids meet.

(*c*) *Guaiacum test.*—A few grains of guaiacum resin are dissolved in 1 c.c. of alcohol, 5 c.c. of urine are added, and a few drops of hydrogen peroxide. If blood is present a blue coloration is produced on standing. The reaction, however, is also positive if pus is present.

(*d*) *Benzidine test.*—0·1 grm. of benzidine is dissolved in 10 c.c. of 50-per-cent. acetic acid. To 2 c.c. of this solution a few drops of urine are added in a dry test-tube. If blood is present a dark green or blue coloration is produced on shaking.

2. Test for Quinine in the Urine

Qualitative test. *Mayer-Tanret method.*—Quinine is in part excreted in the urine, where its presence can be established clinically and very simply by means of an alkaloidal reagent. Giemsa gives the following instructions :

Ten grm. of mercuric potassium iodide are dissolved in 100 c.c. of water and 5 grm. of glacial acetic acid added.

If necessary the reagent can be made in the following way :—Solution 1. Mercuric chloride 27 grm. dissolved in 1,500 c.c. of boiling distilled water ; Solution 2. Potassium iodide 100 grm. in 500 c.c. of cold distilled water. Solution 1 is mixed with Solution 2, and 25 grm. of glacial acetic acid are added ; this yields a stable reagent (Tanret's reagent, Mayer's reagent).

Added to cold urine, a turbidity occurs in the presence of 1 : 200,000 of

quinine. The precipitate dissolves on heating. As the reagent also precipitates albumin, it is advisable, in order to avoid mistakes, to proceed as follows: If the cold filtered urine remains clear after adding the reagent, neither quinine nor albumin is present. If the turbidity appears which disappears on heating, quinine is present. If the turbidity persists when the liquid is heated, albumin is present. If the latter has been removed by filtration and the solution becomes again cloudy on cooling, quinine, in addition to albumin, is present in the urine.

Other alkaloids given in the usual therapeutic doses in addition to quinine need not be taken into consideration in applying this test, but plasmoquine may also give a positive reaction.

3. Tests for Atebrin in the Urine

Qualitative test.—Atebrin can be extracted with ether from the urine after it has been made alkaline, the ether then removed by evaporation, and the residue dissolved in concentrated sulphuric acid; a yellow coloration with marked fluorescence indicates the presence of atebrin. Tropp and Weis elaborated a method for the colorimetric estimation of atebrin by comparison with solutions of known concentration in sulphuric acid.

The more simple method of Wats and Ghosh, modified by Field and Niven, is as follows:—10 c.c. of urine are made alkaline in a test-tube with a few drops of solution of sodium hydroxide; 0·25 c.c. of amyl alcohol is added, and the mixture is well shaken. On separation all the atebrin is found in the upper layer of amyl alcohol. Larger quantities are recognizable, even with the naked eye by the yellow coloration which is seen when the test-tube is viewed by transmitted light against a dark background. In ultra-violet light traces are still recognizable up to a dilution of 1 : 2,500,000 by the typical fluorescence. However, a control test with normal urine is necessary as other pigments are also extracted by amyl alcohol.

VI.—MICROSCOPICAL EXAMINATION OF THE FÆCES FOR EGGS OF INTESTINAL PARASITES

The eggs of the tapeworm and of the common threadworm (*Enterobius vermicularis*) (Plate XXXIII, 19) are rarely found in the stools, as these parasites do not, as a rule, part with their eggs until the joints of the former, or the entire body of the latter, have left the alimentary canal. Occasionally the eggs of hepatic and intestinal parasites, such as *Bilharzia hæmatobia*, *B. mansoni*, *B. japonica* (Plate XXXIII, *11*, *12*, *13*), *Clonorchis sinensis* (Plate XXXIII, *5*), *Fasciola hepatica*, *Fasciolopsis buskii* (Plate XXXIII, *7*), *Heterophyes heterophyes* (Plate XXXIII, *3*), and of rarer helminths, are encountered.

The microscopical examination of fæces for eggs is by no means a difficult matter. All that is necessary, by way of preparation, is to place on the slide a minute portion of the suspected fæces—about the size of a hemp-seed—and then to apply the cover-glass, gently gliding it over the slide so as to spread out the mass in a thin, fairly uniform, and transparent layer.

The points to be attended to in the diagnosis of eggs are size, shape, colour, thickness, roughness, smoothness, and markings on the surface of the shell; the presence or otherwise of yolk spheres, of a differentiated embryo, or, in the case of the cestodes, of the three pairs of embryonic hooklets; the existence of an operculum in the case of certain trematodes and of the broad tapeworms (*Diphyllobothrium*). The eggs of the same species of parasite

vary but slightly, and are in every instance sufficiently stable and definite for correct diagnosis.

Of the three common nematodes—*Trichuris trichiura* (Plate XXXIII, *18*), *Ascaris lumbricoides* (Plate XXXIII, *7*), and *Ancylostoma duodenale* (Plate XXXIII, *14*)—the eggs of the first are the most frequently met with. They occur sometimes in enormous numbers, as many as six or eight specimens being visible in one field of an inch-objective. They form rather striking objects under the microscope. They are oval, measuring 51 to 54 μ by 22 μ, the ends of the long axis of the oval being slightly pointed, and tipped with a little shining projection or plug. Their general appearance suggests an elongated oval tray, the projections at the poles of the ovum representing the handles. They are dark brown in colour, sharply defined, doubly outlined, and contain no differentiated embryo.

The eggs of *Ascaris lumbricoides* are considerably larger (50 to 75 μ by 40 to 50 μ) than those of trichuris. They are also, as a rule, more spherical or, rather, more broadly oval; occasionally they are almost barrel-shaped. Like those of trichuris, they are dark brown in colour from bile-staining, but they are much less sharply and smoothly defined, possessing a coarse thick shell which is roughened by many warty excrescences. The yolk contents are not always easily made out, nor, when made out, can any indications of embryo or segmentation be discovered. In certain instances the eggs are smooth on the surface, the rough outer layer being almost or altogether absent; such are supposed to be unfertilized.

A point of practical importance to be attended to lies in the circumstance that the rough outer layer of the shell of the egg of ascaris is very easily detached, leaving it with a sharp, smooth outline suggestive of some other species of parasite. To obviate this, in mounting fæces it is well to avoid too much gliding of the cover-glass over the slip.

The eggs of *Ancylostoma duodenale* contrast very markedly with both the foregoing, particularly in the matter of colour. Trichuris and ascaris eggs are invariably dark and bile-stained; those of the ancylostome are beautifully clear and transparent, measure 55–60 μ by 32–40 μ, and have a regular, somewhat elongated oval form, with a delicate, smooth, transparent shell, through which two, or four, or eight light-grey yolk segments can be distinctly seen. It is well to search for these eggs soon after the fæces have been passed; otherwise, owing to the rapidity with which, in favourable circumstances, development proceeds, the embryo may have quitted the shell and the egg be no longer visible. The eggs of *Necator americanus* cannot be differentiated from those of *A. duodenale* with certainty. The eggs of *Trichostrongylus colubriformis* also resemble those of *A. duodenale*, but they are relatively larger and contain a fully segmented morula (Plate XXXIII, *15*).

The eggs of *Heterodera radicicola*, which have a characteristic appearance (Plate XXXIII, *22*), have been noted from time to time in the fæces of otherwise normal individuals since their discovery by Kofoid and White in 1919. *H. radicicola* is a common root-parasitic nematode which lives in a variety of plants, such as radishes, celery, carrots, turnips, etc.; it is therefore liable to be encountered in the excreta of individuals who have ingested these vegetables. Of conspicuous asymmetric appearance and size, 95 μ by 40 μ, they might well be regarded in human fæces as an indication of nematode infection of the intestinal canal. A feature of the egg is the presence of two highly refractile, flattened, bluish-green globules at the poles of the embryo.

As a rule they are kidney-shaped, and can pass through the alimentary canal uninjured.

The eggs of the cestodes may be distinguished from those of the nematodes and trematodes by their circular outline and, as a rule, by their smaller size.

The eggs of *T. saginata* and *T. solium* are provided with a single brown-coloured striated outer membrane, which encloses a ciliated six-hooked onchosphere (Plate XXXIII, *16, 17*). On the other hand, *Hymenolepis nana* eggs (40 μ) have two transparent membranes (Plate XXXIII, *20*). Individual eggs of *T. saginata* are more avoid in shape than those of *T. solium*, and measure 30 μ in diameter. The eggs of *Diphyllobothrium latum* (70 μ by 45 μ) are translucent, oval in shape, and provided with an operculum (Plate XXXIII, *21*).

Method of concentrating helminth eggs.—Clayton Lane has devised a technique known as the " floatation method," which has proved accurate and useful in the mass diagnosis of ancylostome and, to a certain extent, other helminth infections, and by the aid of which a diagnosis may be determined in cases where the eggs cannot be found by direct examination of the fæces. The eggs are collected from 1 c.c. of fæces by " direct centrifugal floatation." The aim of the apparatus is to keep fixed upon the centrifuge tube a square glass cover which will collect the floating eggs, and which is held in place by a cover-slip of such a shape as to prevent movement and leakage, and yet permit of the ready removal of the cover for direct microscopical examination, thus making the area of collection and examination identical. (Fig. 361.)

The centrifuge tube is a glass cylinder, 4¾ in. long by ½ in. in internal diameter, closed at the bottom, and with the mouth ground off flat at right angles with the long axis of the tube. The cover is held in position during centrifuging by means of a cover-slip. The centrifuge tube is suspended in a metal bucket of 1½ in. internal diameter. Two such buckets are employed, each containing a centrifuge tube. Fæces (1 c.c.) are first disintegrated by vigorous shaking in water in a closed tube, and centrifuged for one minute at 1,000 revolutions ; the supernatant fluid is decanted, and a solution of salt of a specific gravity of 1150 added, and centrifuging is repeated for thirty seconds at 1,000 revolutions ; the tube should be so filled that the saline lies in contact with the under-surface of the cover-clip. The eggs adhere to the under-surface of the glass, which is carefully removed and examined as a " hanging-drop " preparation.

The direct centrifugal floatation method gives a greater and more reliable concentration than does any other method ; the examination area is about ¼ sq. in., and the whole process is carried through in a few minutes. The eggs of intestinal helminths, other than the ancylostome and trichostrongylus, cannot be concentrated by this method with the same degree of certainty.

Simple floatation method (*Hung*).—Two grammes of fæces are carefully rubbed up with a glass rod and saturated salt-solution ; the mixture is poured into a watch-glass or wide tube which is filled to the brim. A slide or cover-glass is placed in contact with the fluid and allowed to remain for ten minutes. If ancylostome eggs are present they will be found adhering to the under-surface of the slide or cover-glass.

Fülleborn's method for detection of bilharzia eggs in the fæces.—The diagnosis of intestinal bilharziasis by detection of the eggs in the fæces by simple microscopic examination is not always an easy matter. Fæces of the volume of a hazel-nut are placed in a conical glass, carefully rubbed up with a glass rod and a little 2½-per-cent. salt-solution, and put away to settle, in

the dark, for five minutes. The solution is poured off from the sediment, and the process repeated two or three times. The bilharzia eggs remain

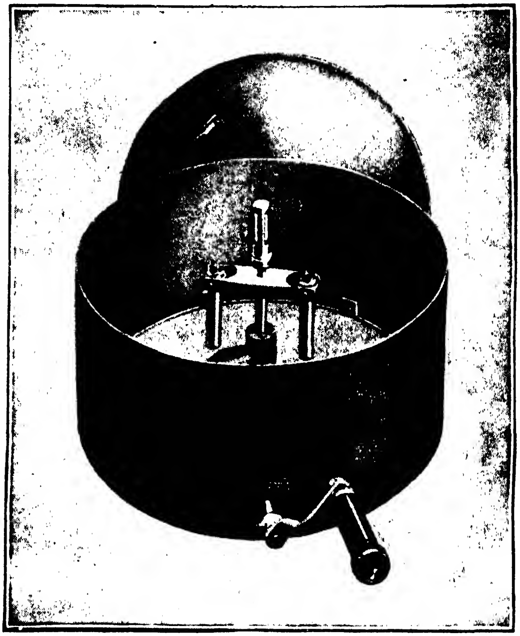
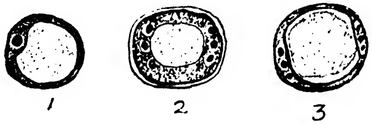


Fig. 361.—Clayton Lane's centrifuge. (*Greatly reduced. As supplied by Messrs. R. B. Turner & Co.*)

in the sediment, which is flooded with distilled water at 120° F. and exposed to a bright light.

The miracidia now escape from the eggs, and can easily be seen with a lens, particularly against a dark background. On adding a few drops of



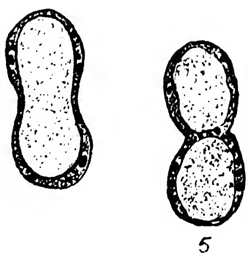


Fig. 362.—*Blastocystis hominis.* × 1,500. (*Orig.*)

1, 2, 3, Resting forms; 4, 5, dividing forms.

perchloride-of-mercury solution, they are killed off and are found in the sediment (*see also* p. 736).

Microscopical examination and recognition of various elements in the fæces (Fig. 362).—*Blastocystis hominis.*—Sometimes during the exam-

ination of fæces, a yeast-like organism simulating an amœbic cyst, but less refractile, is encountered. This is known as *Blastocystis*. (Plates XXIX, XXX). The individual cell contains a large central vacuole, while the cytoplasm is reduced to a thin layer in which are situated one or two small iodophilic nuclei at each pole of the cyst. The cytoplasm contains refractile globules of *volutin* which must not be mistaken for the nuclei. *Blastocystis* multiplies by gemmation and rapidly increases in culture media such as are used for *E. histolytica*, unless dextrose has been added. The organism varies a good deal in size and shape; single cysts measure from 5–20 μ in diameter. *Blastocystis* is likely to be mistaken for a fat-globule or semi-digested muscle-fibre, unless the finer points of structure can be distinguished. This organism has no pathogenic significance so far as is known.

Muscle-fibres, derived from meat, practically always occur in the stools, and are recognized by their cross-striation. When present in large numbers they indicate defective intestinal digestion. (Fig. 363, *2*.)

Connective tissue, derived from meat, resembles mucus somewhat; it is distinguished by striation, which disappears on addition of acetic acid. When it is present in large masses, defective gastric digestion may be inferred. Elastic fibres have no significance.

Starch granules, derived from fruit and potatoes, are stained blue by addition of iodine solution. They vary in size and shape, according to the food from which they are derived. Well-preserved granules with concentric markings are seldom seen. They are often enclosed in a cellulose covering, but are not liable to give rise to much difficulty, except those derived from peas and beans, which roughly resemble the eggs of tapeworms.

The presence of excess of starch is pathological, and such a stool is usually acid and shows signs of gas-bubbles, fermentation, and presence of yeasts. It is an interesting point that starch is never bile-stained. The iodine test may be applied to ascertain the extent to which the starch has been digested. A blue colour indicates unchanged granules; red, that they have been slightly digested.

Detritus which is derived from fruits and vegetables is easily recognized by its spiral ducts, areolar tissue, vascular bundles, and pigment cells.

Neutral fats, derived from the fat of food, are recognized as colourless, highly refractile droplets, or sometimes as irregular bile-stained masses which are stained by Sudan III and are soluble in ether.

Fatty acids, derived from the fat of food, occur as sheaves of colourless acicular crystals, which melt on being warmed and dissolve in ether. (Fig. 363, *4*.)

Soaps, derived from the fat of food, occur as greasy-looking amorphous masses, or sometimes as needles which are thicker and not so long as those of the fatty acids. They may be colourless, or stained with bile-pigments. They are not soluble in ether, as are the fatty acids, and do not melt on being warmed. If the film of fæces on a slide is treated with acetic acid and heated, fatty-acid crystals will be seen to separate out. (Fig. 363, *3*.)

Fats may be distinguished from mucus or from vegetable material by the following rough test: Prepare a smear of the stool on a slide, put on a cover-slip, and press the latter down on to the smear: should the material be of fatty composition, the cover-slip will remain down; if vegetable detritus or mucus, it will spring back when the pressure is taken off. (Fig. 363, *1*.)

In a normal stool, fat is present almost entirely in the form of amorphous masses of soap, less often as crystals. Neutral fat ought to be absent.

Mucus occurs as transparent shreds, sometimes bile-stained. It has always a pathological significance and, when containing leucocytes and epithelial cells, indicates intestinal ulceration.

Intestinal sand.—The appearance of sand grains in the stools of persons

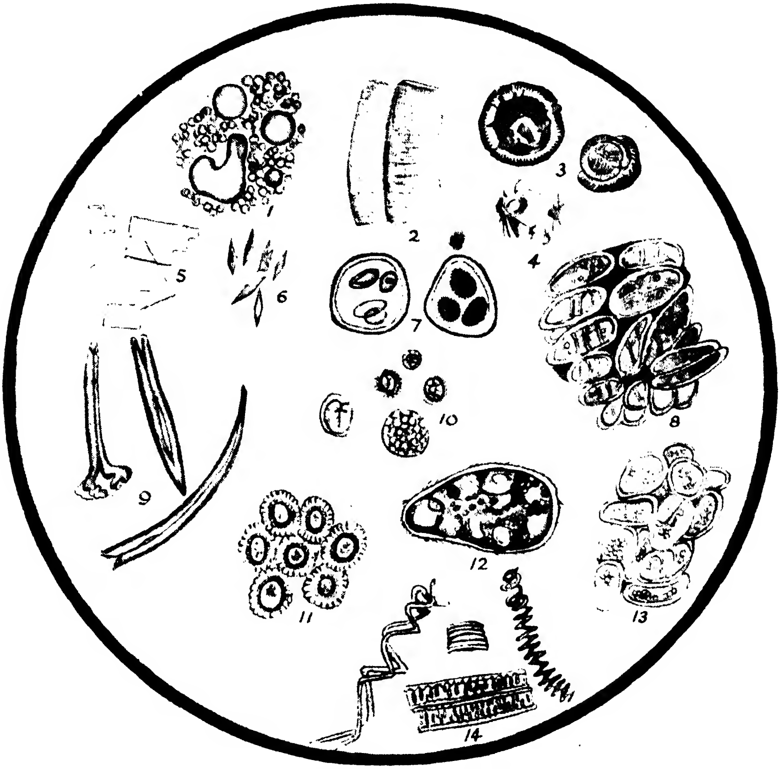


Fig. 363.—Microscopic appearance of common objects in the fæces. × 800 diam. (*Orig.*)

1, Casein and fat droplets; 2, muscle-fibres; 3, soap crystals; 4, crystalline fatty needles; 5, cholesterin crystals; 6, Charcot-Leyden crystals; 7, truffle spores; 8, portions of husks of cereals, 9, hairs of wheat grain; 10, spores of fungi; 11, cells from pericarp of peas; 12, parenchyma of beans; 13, endosperm of rice; 14, vegetable spirals.

who live where desert conditions exist is extremely frequent, and is due to the ingestion of this substance with food.

Charcot-Leyden crystals are frequently found in stools containing entamœbæ. (Fig. 363, *6*.)

Pseudo-parasites.—It frequently happens that orange-pulp is mistaken for trematodes, banana fibres for small tapeworms, pieces of cotton-thread and celery for *Enterobius vermicularis*, *Ancylostoma duodenale*, etc. As regards the microscopic diagnosis, numerous objects may be mistaken for helminthic

eggs, and it is important that the tropical worker should be able to recognize various articles of diet as they appear in the stools. The spores of truffles, which occasionally are seen in the fæces, may be mistaken for eggs of *Ascaris lumbricoides*, owing to their size (42-66 μ) and rough surface. (Plate XXXIII, 7.) The spores of mushrooms have a similar appearance. Pollen grains of plants and spores of fungi have given rise to difficulties, in spite of their characteristic appearance under the microscope. It should be borne in mind that the pollen of conifers is often met with in the stools of people living near pine forests. No difficulty will be experienced in diagnosis when it is remembered that all these spores are really globes with a reticulated surface which can be made out on careful focusing. (Fig. 363, *10.*) Occasionally cheese-mites and their eggs may be found in the fæces after being ingested with the food.

Demonstration of protozoa in fæces.—It is difficult to make out the nuclear details of the intestinal protozoa and their cysts in a fresh state. The addition of Weigert's iodine solution (iodine 1 part, pot. iod. 2 parts, water 100 parts), which has a special affinity for nuclear structure, and which renders the details much more evident, constitutes a convenient method for their recognition. (Plate XXX.)

Method of concentration of protozoal cysts in fæces.—Yorke has devised the following method of concentration especially applicable to the cysts of *Entamœba histolytica*:

A mass of fæces is ground up with water in a small mortar and the emulsion shaken with 500–1,000 c.c. of water, poured into a tall glass cylinder, and allowed to stand for fifteen minutes to permit the coarser fæcal material to settle. The supernatant fluid is withdrawn and centrifuged, and the deposit is shaken up with a solution of cane-sugar of specific gravity of 1080 and again centrifuged quickly. This procedure results in the separation of cysts from the remaining fæcal material. The fæces are precipitated and the cysts left floating in the supernatant fluid, which is withdrawn, diluted with about four times its volume of water, and again centrifuged at high speed. By this means a small deposit is obtained consisting of great numbers of cysts in a relatively minute quantity of fæcal material. The deposit is then washed several times with water to get rid of all traces of sugar and the majority of the remaining bacteria.

In addition to the iodine method of demonstrating protozoa in fæces, the following methods of staining are recommended by Dobell:

Thin films of fæces are made on cover-slips and floated film downwards on the fixing fluid.

Method I

(1) Fix films for 10–20 minutes in Schaudinn's fluid.[1]
(2) 70-per-cent. alcohol, two changes.
(3) 70-per-cent. alcohol and iodine (Lugol's solution, 1 drop), 10 minutes.
(4) Distilled water after hyposulphite-of-soda solution (1 crystal in 25 c.c.).
(5) Hæmalum (Mayer's) 15–20 minutes.
(6) Running water till blue.
(7) Through alcohols, alcohol and xylol, xylol.
(8) Mount in Canada balsam.

[1] Absolute alcohol 50 c.c., saturated solution of corrosive sublimate 100 c.c., glacial acetic acid 1–5 c.c.

Method II

1-per-cent. hæmatein in 70-per-cent. alcohol = stain.
Iron alum in alcohol = mordant.[1]

(1) Fix films in Schaudinn's fluid as before for 10–20 minutes.
(2) Wash in 70-per-cent. alcohol.
(3) 70-per-cent. alcohol and iodine, 10 minutes.
(4) Mordant, 10 minutes.
(5) Alcohol, 70-per-cent., several changes.
(6) Stain, 10–20 minutes.
(7) Wash in 70-per-cent. alcohol.
(8) Differentiate with mordant under microscope.
(9) 70-per-cent. alcohol, several changes.
(10) Absolute alcohol, two changes.
(11) Absolute alcohol and xylol.
(12) Xylol.
(13) Mount in Canada balsam.

VII. DIAGNOSIS BY AGGLUTINATION WITH PATIENT'S SERUM FOR TYPHOID, PARATYPHOID, DYSENTERY AND BRUCELLA INFECTIONS

A. Agglutination by Garrow's agglutinometer is a practical method suitable for small laboratories and for rapid and ready diagnosis.

For use the following apparatus is required:

(1) *A painter's palette* for dilution of the serum. (2) A *diluting pipete* drawn from glass tubing ¼ in. in diameter and 6 in. in length. The latter should deliver a drop of satisfactory dimensions (a Donald's pipette fitting Morse gauge No. 70 is the correct size)—that is, when mingled with an equal quantity of bacterial emulsion, it should not run over the edge of the glass slab. (3) The *agglutinometer slab*, a piece of plate glass 11¾ in. long by 1½ in. wide, divided into a number of partitions by double grooves running at regular intervals of 1 cm. in order to prevent the dilutions from intermingling. (4) *Set of bacterial emulsions*. The stock emulsions for use with the agglutinometer for the diagnosis of enteric are *B. typhosus*, *B. paratyphosus* A, B, and C; for undulant fever, *Brucella melitensis* and *Br. abortus*, for bacillary dysentery, *B. shiga*, *B. flexner*, and *Sonne*. They are made from 24-hour surface agar cultures. The growth is scraped (not washed) off the surface by means of a platinum loop and emulsified in 0·2-per-cent. formalin in normal saline. The emulsions should be very dense, of milky consistence and uniform suspension.

In order to promote the intimate mixture of the serum under investigation and the bacterial emulsions, the slab is made to revolve by means of clock-work at a uniform rate of about 15 revolutions per minute. For field use the slab may be placed in a simple box provided with damp blotting-paper in order to obviate desiccation, and turned by hand with an iron handle attached to a wooden shaft which supports the glass slab.

The diluting process.—The blood for examination is taken from the finger and collected in a capsule. Three large drops of blood are sufficient; the ends of the tube are sealed with wax or plasticine. After standing for some

[1] Dissolve 1 grm. of iron alum in 2 c.c. distilled water, and add 77 c.c. of 96-per-cent. alcohol.

time the serum separates, rendering centrifugalization unnecessary. By means of the pipette, 2 drops of clear serum are abstracted and placed in the first partition of the mixing palette. In order to make a dilution of 1 : 5, 8 similar drops of normal saline are added. From the resulting 10 drops of diluted serum, 5 are then placed in the next partition and a similar amount of saline added; and so on, thus making a series of dilutions from 1 : 5 to 1 : 80 or higher. It is important that the pipette be held vertically throughout the process, to ensure equality in size of the drops.

B. A simple method of macroscopic agglutination **by progressive dilution of the serum** in agglutination tubes can be employed, but gives only a limited range of dilution, and a considerable amount of blood (1–2 c.c.) is required. The glass capsules containing the blood should be centrifuged, and the serum abstracted by means of a pipette. At least 5 drops of clear serum are required in order to obtain a quantity sufficient for further dilution. This amount should be mixed with 20 drops of normal saline delivered from the same pipette held in a vertical position, in order to obtain a 1 : 5 dilution. For further dilution, 20 drops of the 1 : 5 dilution are placed in the first of a row of agglutination tubes, after which 10 drops are removed and mingled with an equal amount of saline in the second tube, thus giving a dilution of 1 : 10. From these 20 drops, 10 are removed and placed in a third tube, and so on; the dilution each time being doubled. To the 10 drops of diluted serum remaining in each tube an equal amount of an opalescent emulsion of bacilli should be added, thus doubling the dilution of the suspension in which the organisms are placed. The tubes are incubated for 2½ hours or, preferably, for a shorter period at 55° C., and are then examined for agglutination against a dark background; this is generally sufficiently obvious when compared with control tubes in which bacillary emulsion diluted with saline or with normal serum has been placed. The objection to this method is the limited range of titre which it affords; in order to get a range of from 1 : 10 to 1 : 160, a row of five tubes is necessary.[1]

In testing for typhoid and paratyphoid agglutinins, three rows of five tubes each are necessary—one for typhoid, and one each for paratyphoid A and B.

In describing the various methods, the following abbreviations are commonly used, viz. "T" for typhoid, "A" for paratyphoid A, "B" for paratyphoid B, and "C" for paratyphoid C.

C. A more accurate method is **Dreyer's drop method,** for which standardized bacillary emulsions can be obtained. The standard culture is as sensitive to agglutination as is the fresh culture; it is, moreover, sterile and, if stored in a cool, dark place, can be kept indefinitely.

The highest dilution in which marked agglutination, without sedimentation, occurs and can be detected by the naked eye, is termed *standard agglutination.* When this occurs with *standard agglutinable cultures* in a serum diluted to a certain degree, then the latter figure, divided by the number given on the label of the culture employed, gives the number of *standard agglutination units* contained in 1 c.c. of the serum examined.

A stand containing 15 small agglutination tubes in three rows of five each, and two larger dilution tubes, should be taken. With a dropping pipette measure out into one large dilution tube 54 drops of normal saline solution (0·85-per-cent. sodium chloride in distilled water) by means of gentle pressure

[1] The principle of the bacterial emulsions issued from the Oxford laboratories under the auspices of the Medical Research Council are formolized with cultures of strains frequently subcultured to increase their agglutinability. They remain stable for long periods.

on the teat. Wash the pipette with distilled water, and subsequently with absolute alcohol and ether, so as to dry thoroughly. Take up the serum to be tested into the dried pipette. Measure out 6 drops of the serum into the dilution tube already containing the 54 drops of saline, thus obtaining a dilution of 1 : 10.

The second tube should be taken, and 3 drops of the 1 : 10 serum dilution added to 57 drops of normal saline; this gives a dilution of 1 : 200. The pipette should be carefully washed out, and to each tube in the row 15 drops of standard agglutinable emulsions of T, A and B are added. Thus:

① ② ③ ④ ⑤	① ② ③ ④ ⑤	① ② ③ ④ ⑤
T	A	B
15 drops	15 drops	15 drops

For the addition of the diluted serum it is best to commence with the higher dilutions before proceeding to the lower ones. To tube 3 in each row add 10 drops of 1 : 200 serum; to tube 4 in each row add 5 drops of 1 : 200; to tube 1 add 10 drops of 1 : 10 dilution, and to tube 2 also add 2 drops of 1 : 10 dilution. The pipette must be washed out before proceeding to add the saline. The addition of saline should then be made to tubes 2 and 4, which receive 8 and 5 drops respectively, while tube 5 receives no serum, but 10 drops of saline only, and acts as a control against spontaneous agglutination. This can be best represented by the following scheme:

No. of tube	*Drops of normal saline*	*Drops of serum*
		Dilution of 1 : 10
1	0	10
2	8	2
		Dilution of 1 : 200
3	0	10
4	5	5
5	10	0

It will be noted that the final volume of fluid in each tube, when the bacillary emulsions are added, is 25 drops. By mathematical calculation it will be seen that in tube 1 of each row the serum acts in a dilution of 1 : 25.

In tube 2 in a dilution of 1 : 125
,, 3 ,, ,, 1 : 500
,, 4 ,, ,, 1 : 1,000

The tubes are examined after four hours at 37° C., or two hours at 50°–55° C., followed by fifteen minutes at room temperature. The reading is taken by comparing each tube in succession with the control tube, and it preferably made by means of artificial light against a black background. If daylight is used, the tubes should be partly shadowed by passing a finger up and down behind them.

The agglutinins of *Brucella melitensis* and *Br. abortus* sometimes do not appear in the blood until the third or fourth week of the disease. Attention must be paid to a curious phenomenon called the *inversion phenomenon*. For instance, agglutinins may be demonstrable in the higher but not in lower dilutions. In *Brucella* infections, a dilution of 1 : 50 or over may be regarded as diagnostic.

Strains of *Brucella abortus* (Bang) may be agglutinated in high dilutions by patients suffering from undulant fever (*Br. melitensis*) (*see* p. 326).

Certain authorities recommend that the serum of undulant-fever cases should be heated to 56° C. for half an hour before it is tested to eliminate any non-specific agglutinins which may be present, and this is especially applicable to fever of the *Br. abortus* type, as the agglutinins of this organism can be absorbed by drinking infected milk.

GENERAL MODERN CONCEPTIONS ON ANTIGENS

The effects of heat on the various agents concerned in agglutination has revealed differences in the heat stability of different bacterial antigens[1] (agglutinogens), and of the reacting agglutinins. There are *heat-labile* antigens which cease to react with the corresponding agglutinins after being treated for one hour at temperatures varying between 62° and 75° C. A second group of antigens are *heat-stable.*

In many instances, certain differences in the character of the clumps formed during flocculation are noted. The interaction of heat-labile agglutinogens and the corresponding agglutinins leads to the formation of loosely-knit clumps, like flakes of snow. which form a bulky precipitate but which are readily broken up on shaking. On the other hand. the interaction of heat-stable agglutinogens with the corresponding agglutinins leads to the formation of smaller but tighter clumps which settle as a granular deposit and which are not easily redispersed by shaking. The heat-labile antigens and their antibodies are known as " H," while the symbol " O " is used for the heat-stable antigens. Any agglutinin which is produced in response to the inoculation of a particular agglutinogen is regarded as homologous with it. Heterologous strains can be distinguished by serological methods which demonstrate differences in their antigenic components. It was therefore considered possible to estimate quantitatively the antigenic content of a given serum, and further to distinguish agglutinins due to inoculation from those produced as a result of direct infection with living bacteria. The heat-labile " H " agglutinogens are associated with the flagella of the bacteria, while the heat-stable (somatic) " O " agglutinogens are contained in the bacillary bodies. (For recent developments in the diagnosis of typhoid see pp. 338, 339.)

VIII.—PREPARATION OF SPECIAL CULTURE MEDIA

Nicolle, Novy, and MacNeal medium (N.N.N.), for cultivation of leishmania and other protozoa.—*Composition :*

Agar	14 grm.
Sodium chloride	6 ,,
Water	900 c.c.

The agar and the sodium chloride are added to the water in a flask, well shaken, and dissolved by steaming for two hours. The hot solution is then

[1] The particular component of the bacterial substance which provides the specific stimulus is usually termed an *agglutinogen*; thus one antigen may comprise several different agglutinogens.

filtered through cotton-wool, and about 3 c.c. are afterwards distributed into each of 50 test-tubes and sterilized in the autoclave at 120° C. for 20 mins. The medium is cooled to 55° C., and into each tube are dropped 20 drops of whole rabbit's blood as described in connection with the Noguchi-Wenyon medium (*see* below).

The tubes are "rolled" in the hand and "sloped" upon a glass rod. When the agar has set, they are incubated for twenty-four hours to test for sterility and to allow them to "sweat." They are now capped or sealed with paraffin wax. Inoculation is effected by introducing suspected material into the "water of condensation"; the tubes are kept at 22° C. and examined 5–7 days later for developmental forms of protozoa.

Adler's medium for the cultivation of leishmania, etc.—Locke's[1] solution is placed in test-tubes in amounts of 4·5 c.c.; the tubes are placed in a waterbath and the temperature is raised to 100° C. when 0·5 c.c. of 2-per-cent. nutrient agar is added to each tube and the mixture sterilized in a Koch's steamer for one hour on three successive days. When cool, 0·5 c.c. of sterile rabbit's serum is added to each tube.

Noguchi-Wenyon medium for the cultivation of spirochætes, leptospira and certain protozoa.—The medium is prepared as follows: To 270 c.c. of 0·85-per-cent. sodium chloride add 30 c.c. of ordinary 2·5-per-cent. nutrient agar, pH 7·6. When thoroughly mixed, place 9 c.c. in each tube. After being autoclaved at 120° C. for half an hour the tubes are cooled to 55° C., and into each tube are dropped, from a rabbit's ear, 20 drops of blood. The tubes, which are not shaken, are incubated for twenty-four hours. The medium is then ready for use.

The blood is obtained from the rabbit by the paraffin method. The animal is enclosed in a box at one end of which is a round aperture fitting the neck, through which the head projects. The ear is shaved over the marginal vein and is wiped over with alcoholic iodine solution. When dry, the ear is coated above, below, and on the margin with hot melted paraffin wax, so that the area of operation is covered with a thin layer through which the vein is still visible. The base of the marginal vein is clamped with a "bull-dog" clip, with a sharp knife an incision is made in the vein, and the sterile blood is allowed to drop from the paraffined margin of the ear into the tubes. After incubation of the blood-agar tubes it will often be found that the blood has coagulated in a cylindrical column, leaving a clear agar medium around it.

In this medium *Leptospira icterohæmorrhagiæ* grows readily, and sub-culture requires to be made once every three or four weeks.

The medium has also been employed for the culture of certain intestinal protozoa, such as *Embadomonas intestinalis*, the flagellates growing in association with numerous bacteria, but for success with leptospira absolute sterility is essential.

Boeck and Drbohlav's medium for the cultivation of *Entamœba histolytica*, etc.—Three whole eggs are gently beaten and poured into a clean measure with one-fourth volume of Locke's solution (sodium chloride 9 grm., calcium chloride 0·24 grm., potassium chloride 0·42 grm., sodium bicarbonate 0·2 grm., glucose 2·5 grm., distilled water 1,000 c.c.). The mixture is tubed and sloped. The tubes are placed in a slanting position in the inspissator and the temperature is gradually raised to 60° C. for one

hour. After a second inspissation for a similar period on the second day, the temperature is gradually raised on the third to 80° C. for one hour.

A second solution is made as follows: To 1,000 c.c. of Locke's solution the whipped white of one egg is added; the liquid is mixed and filtered through a "candle." The reaction should be about pH 7·6.

In order to make a culture, 5 c.c. of the albumin solution are added to one of the egg-slants and placed in a water bath at 37° C. for a few minutes. A small portion of fæces is then emulsified in the solution contained in the prepared tube and incubated at 37° C. for twenty-four hours.

Brumpt has advocated the addition of a small quantity of finely-powdered rice-starch to the medium upon which the entamœbæ feed and thrive. The starch is added at the time of inoculation.

To examine the culture, a fairly wide-bore pipette fitted with a rubber teat is used and a small quantity of the deposit at the bottom of the egg column removed.

Serum modification of the above method.—Dobell and Laidlaw advocate a serum slope instead of the egg slope. They state that sub-cultures need only be made every fourth day. To 100 c.c. of distilled water previously warmed to 40° C., 8 grm. of Loeffler's dehydrated blood-serum is added. The dissolved serum is distributed into test tubes, 5 c.c. in each; the tubes are placed in a slanting position and are inspissated on three successive days for one hour. On the third day the temperature is raised from the usual 50° to 100° C. Albumin solution is added to the top of the slope just before use. Rice starch may also be added.

IX.—METHODS OF PRESERVING HELMINTHS AND THEIR EGGS

Trematodes.—The flukes should be collected into a test-tube containing 1 in. of 0·85-per-cent. saline. This should be shaken vigorously for several minutes in order to stun them and render them flaccid. When extended they should be killed by the addition of an equal quantity of a saturated solution of mercury perchloride ($HgCl_2$). The flukes should then be washed in plain water for 20 minutes. For storage purposes they must be placed in tubes containing 70-per-cent. alcohol.

Cestodes.—After removal from the stool, tapeworms should be allowed to relax in water—a process which may last two 2–24 hours, according to the size of the worm. They are then killed and fixed in hot Schaudinn's fluid (*see* p. 1035). After fixation, wash in water for 1–24 hours, according to the size of the specimen, and subsequently store in 70-per-cent. alcohol.

Nematodes.—These should be collected into 0·8-per-cent. saline solution, not into plain water. After removal of fæcal matter by shaking, they should be dropped into 70-per-cent. alcohol heated to 80° C., to which has been added 5 per cent. glycerin. When cool, they may be stored in this same solution.

Eggs of trematodes, cestodes, and nematodes.—A small portion of the stool containing the eggs should be thoroughly mixed by stirring with an equal quantity of Langeron's lactophenol (phenol 1 part, lactic acid 1 part, glycerin 2 parts, water 1 part). Permanent microscopic preparations of eggs in this medium may be made by ringing the cover-glass with the following preparation, which should be applied after melting by heat: Beeswax 3 parts, Venetian turpentine 1 part; or with "seccotine."

X.—SCALES AND STANDARDS

Centigrade and Fahrenheit scales.—To convert Fahrenheit into Centrigrade, subtract 32, multiply the remainder by 5, and divide the result by 9.

To convert Centigrade into Fahrenheit, multiply by 9, divide by 5, and add 32.

The diagram (Fig. 364) shows the relation of Fahrenheit to Centigrade degrees.

Relation of the Metric to the Imperial Standard

Standards of mass

1 milligramme	=	0·015 grain approximately.
1 centigramme	=	0·154 ,, ,,
1 decigramme	=	1·543 grains ,,
1 gramme	=	15·432 ,, ,,
1 kilogramme	=	35 oz., 120 grains, or 15,432 grains.

Standards of capacity

1 cubic centimetre	=	17 minims approximately.
1 litre	=	35 fl. oz., 1 fl. dr., 34 min. approximately.

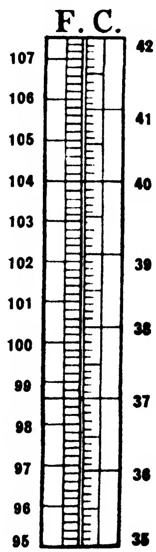


Fig. 364.
Fahrenheit and Centigrade scales compared.

Standards of length

1 Millimicro millimetre ($m\mu$)	=	0·001
1 micron (μ)	=	0·001 millimetre, or 0·000039 inch.
1 millimetre	=	0·039 inch.
1 centimetre	=	0·393 ,,
1 decimetre	=	3·937 inches.
1 metre	=	39·37 ,, nearly.

Factors for converting from one scale to the other

To convert	grammes	into grains	×	15·432
,, ,,	,,	,, ounces	×	0·03527
,, ,,	kilogrammes	,, pounds	×	2·2046
,, ,,	grains	,, grammes	×	0·0648
,, ,,	ounces	,, grammes	×	28·35
,, ,,	cubic c.c.	,, ounces	×	0·0352
,, ,,	litres	,, ounces	×	35·2
,, ,,	ounces	,, cubic c.c.	×	28·42
,, ,,	pints	,, litres	×	0·568
,, ,,	metres	,, inches	×	39·37
,, ,,	inches	,, metres	×	0·0254

Conversion of Imperial to Metric Standard

Mass

$\frac{1}{100}$ grain	×	0·0006	gramme.
$\frac{1}{50}$,,	×	0·0012	,,
$\frac{1}{8}$,,	×	0·008	,,
$\frac{1}{6}$,,	×	0·01	,,
$\frac{1}{4}$,,	×	0·016	,,
$\frac{1}{3}$,,	×	0·02	,,
$\frac{3}{4}$,,	×	0·05	,,
1 ,,	×	0·06	,,

Capacity

1 minim	×	0·06	c.c.
60 ,, ʒi	×	3·55	,,
480 ,, ℥i	×	28·42	,,

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